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THE CONTOUR OF THE PRESSURE CURVE IN THE PULMONARY ARTERY[1]

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I. Introduction

PRECISE records of the pressure changes in the pulmonary vessels have, to the writer's knowledge, not been published. From a woman whose sternum had been removed, Tigerstedt,[2] in 1908, recorded a thoracic pulsation which might possibly be attributed to the pulmonary aorta. In a previous communication the writer reported records inscribed by a Hürthle membrane manometer. These revealed, principally, a low pressure pulse the essential characteristics of which were somewhat modified by inspiration and expiration. It is now recognized, however, that such records obtained by manometers of long vibration periods fail to disclose the detailed changes.

II. Methods — Apparatus

Photographic registration of the pressure changes with a manometer of high frequency and adequate sensitiveness are

[1] The second of a series of studies on the pulmonary circulation, the first of which was published in this journal, volume xxx, p. 233, 1912.

[2] Tigerstedt: Skandinavisches Archiv für Physiologie, 1908, xx, p. 249.

conveniently obtained both in "open" and "closed" chest experiments by the manometer shown in Fig. 1.

This instrument is constructed almost entirely of glass, which facilitates the recognition and removal of air bubbles. It is composed of a vertical manometer tube (*A*) [1.9 cm. in diameter, 8 cm. long] closed above by a stopcock with a bulb and ending below in a canula (3.5 mm. internal diameter, 3 cm. long) which projects downward from the manometer tube at an angle of 140°. Five centimetres from the bottom of the manometer tube a short lateral side tube (*B*) is fused in such a way that it projects slightly into the lumen. The site of this is so chosen that a line crossing the vertical diameter of the opening is 45° to the left of an imaginary line projected vertically upward from the canula junction. Over the opening of side tube (*B*) is cemented a brass cap tapering to and ending in a segment capsule (3mm. in diameter) whose chord side is directed downward (*D*).

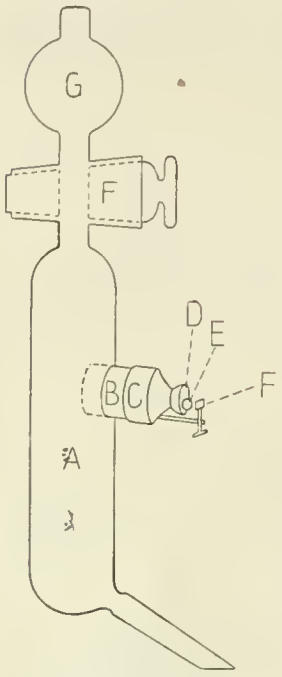

FIGURE 1. Diagram of manometer. Description in text. For clearness the size of the segment capsule is drawn relatively too large.

The manometer is filled to the exclusion of even the most minute air bubbles, by connecting the canula with a pressure or gravity bottle, after which the upper stopcock is closed and the manometer clamped horizontally. A piece of rubber dam is stretched and tied over the segment capsule. Upon this rubber a small plane mirror (*E*) [2 mm. in diameter and 0.2 mm. thick, Carl Zeiss] is glued, after the method described by Frank [1] so that its diameter pivots very exactly on the chord side of the capsule. Except when in use, the mirror is protected by a cap screwing over the entire segment capsule, an important feature in operative work.

The manometer was especially planned for convenient use in the artery of the lower lobe of the right lung but can be utilized in other lung vessels. The isolated lung vessel is ligated

[1] FRANK: Tigerstedt's Handbuch der physiologischen Methodik, 1913, ii[4], p. 28, ii[2], p. 94; Zeitschrift für Biologie, 1913, lix, p. 526.

peripherally and compressed with the finger centrally. The canula is then slipped into the vessel to the constriction and securely tied. This brings the end of the canula well toward the main pulmonary artery, the lateral pressure in which can be recorded free from the distortions which respiratory movements often cause due to the kinking of the artery about short-necked canulas. In some of the experiments the chest was subsequently repaired and the animal resumed natural breathing as described in the previous paper. In these cases the lateral tube and segment capsule just projected from the chest wall. In all experiments care is taken to maintain a right auricular pressure equal at least to intrathoracic. The manometer is immovably clamped by a burette clamp securely attached to and reinforced by heavy iron supports mounted on cement pillars. A horizontal band of light of suitable width is created by an adjustable slit fixed before a small arc lamp (4 amperes, 110 volts; Leitz & Co.) and the image focused for the recording camera by a convex lens equipped with an iris diaphragm. The beam is concentrated upon the small mirror in such a way that the incident and reflected rays form as acute an angle as circumstances permit. The small image of the band, thus reflected back, falls upon a second reflecting mirror (6 cm. in diameter) mounted so as to be vertically and horizontally movable by fine adjustments. By this mirror it is possible to throw the image to any portion of the vertically placed cylindrical lens of the photographic camera. The intensity of the arc light is sufficient for all purposes and all speeds of paper motion which is not the case with the Nernst filament employed by Frank.

Since slight movements of the manometer are much less readily avoided with optically recording manometers and when present are enormously magnified, it becomes necessary to record simultaneously with the pressure changes some base line that shall follow all accidental movements and, in relation to which also, pressures can be established by calibration. In the present instance this is accomplished by a second small mirror (*F*, Fig. 1) mounted by a tiny adjustable support. This mirror can be so rotated that it divides the horizontal beam of light with the movable mirror on the membrane and reflects it just

above or below the latter on the reflecting mirror. By adjustment of the reflecting mirror the two bands in their up and down movements remain equidistant. Extraneous movements of the manometer also affect both reflected beams alike. Calibration involves two stages. The sensitiveness is determined before or after the experiment by clamping the vessel peripherally and allowing definite pressure to play upon the membrane by opening the glass stopcock (*F*) and recording these on a moving drum. During an experiment the relation of the zero level to the base line is determined by clamping the artery, opening stopcock (*F*) and bringing the fluid level at end of a tube connecting with a glass bulb (*G*) to the same level as the end of the canula in the artery.

FIGURE 2. Vibration tests of manometer. Upper record, tuning fork .02 second.

Through stopcock *F* a small amount of fluid is occasionally forced into the manometer and artery which effectually prevents clotting, a serious and persistent occurrence in the pulmonary circuit with other manometers.

The manometer was covered in the experiments with rubber $\frac{17}{1000}$ inches in thickness. Calibration showed that the sensitiveness was such that a record of two millimetres equalled one millimetre of mercury pressure, varying somewhat, of course, with the tension of the rubber during different experiments. Oscillation tests (Fig. 2) showed that the instrument had an inherent rate of 158 per second (T = .00636). This rate could, of course, be increased by sacrificing sensitiveness, but, inasmuch as it was entirely adequate and great sensitiveness was desirable, this was not deemed necessary.

III. Description of Records

The normal pressure curve. — In their essential features, the curves obtained in "open" and "closed" chest experiments agreed with each other and, in their fundamental features, with the aortic pressure curves described by Frank.[1] It will serve our purpose best, therefore, to review briefly the pressure waves described by this investigator and to compare with them the corresponding waves in the pulmonary circuit. Frank[1] describes first, a series of preliminary waves or "Vorschwingungen," (Fig. 3, *A*) of which the wave 1–2, synchronous with auricular systole, is characterized by a slow rise and an equally slow fall. When aortic pressure is low, it terminates in a sudden drop of pressure (wave 2–3, Fig. 3, *A*). Frank explains the wave from 1 to 2 as due to an increase in intraventricular pressure by auricular contraction, which, though slight, is transmitted through the aortic valves because the relatively low pressure at this stage of the cardiac cycle insures a correspondingly low elasticity coefficient of the aortic valves. Thus is explained the fact that this wave is less distinct or disappears entirely when aortic pressure is high. Upon the same theory, the rapid drop (2–3) would signify a movement of the valves into the ventricle, incident to a lower ventricular pressure. In view of the fact that no adequate intraventricular pressure curve at that time had been recorded, this interpretation was only tentatively adopted by Frank who also recognized the possibility of an extra-cardiac influence. This negative depression (.005 second to .01 second in duration) was followed by an oscillation (3–5) varying from .0166 to .03 second. This wave Frank explained as follows: The aortic valves are under a tension proportional

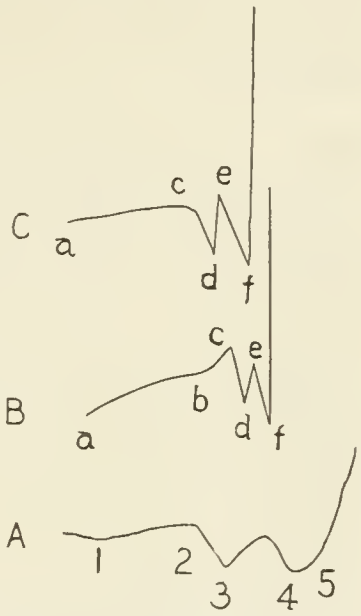

Figure 3. Preliminary vibrations (Vorschwingungen) *A*, in the aortic system after Frank, *B* and *C* in the pulmonary artery enlarged and transcribed from waves of Fig. 4. Figures and letters referred to in text.

[1] Frank: Zeitschrift für Biologie, 1905, xlvi, p. 478.

to the difference between the arterial and ventricular pressures. When the ventricular pressure rises suddenly during the isometric period, 'Anspannungszeit,' the valve tension decreases because the pressure difference on the two sides diminishes and the valves bulge toward the arterial side. This bulging can occur only by a movement of the arterial column and as it occurs very rapidly, we obtain a vibration. According to Frank, this vibration measures the period of rising tension in the ventricle previous to the opening of the semilunar valves (Anspannungszeit).

In the preliminary vibrations of the pulmonary artery similar variations are discerned (Fig. 3, *B*, *C*). The wave $a-b$ evidently corresponds to the auricular contraction. In many cases this is followed by an elevation $(b-c)$ before the negative wave $(c-d)$ supervenes. This in turn is followed by the short vibration $(d-e-f)$ after which the main rise occurs. A study of curves enlarged and transcribed to millimetre paper after a method similar to that described by Broemser[1] leads to the conclusion that the true "Anspannungszeit" falls during the waves $c-d-e-f$ and that the wave $b-c$ when present, is concerned with auricular pressure changes. The negative wave $(c-d)$ present in the aortic curve only during low pressure is always clearly distinguishable in the pulmonary arterial record. Its causation cannot be definitely indicated but the explanation of Frank is scarcely satisfactory, for the intraventricular pressure curves taken with optically recording manometers of Straub[2], Piper[3], Tigerstedt[4], and the writer[5] fail to show any corresponding drop of intraventricular pressure following the auricular pressure wave.[6]

[1] Broemser: Zeitschrift für biologischen Technik und Methodik, 1912, ii, p. 322.

[2] Straub: Archiv für die gesammte Physiologie, 1911, cxliii, p. 69.

[3] Piper: Zentralblatt für Physiologie, 1912, xxvi, p. 429; Archiv für Physiologie, 1912, p. 343.

[4] Tigerstedt: Skandinavisches Archiv für Physiologie, 1912, xxvii, p. 36.

[5] Wiggers: Proceedings of the Society for Experimental Biology and Medicine, 1913, xi, No. 5 (822).

[6] It should now be added that a very similar negative wave in the intraventricular pressure curve has been obtained since the above was written. The explanation of Frank gains by this observation.

This change may, however, be interpreted as a mechanical traction upon the large vessels at the very beginning of ventricular systole, for a downward movement of the aorta and pulmonary artery has been recorded synchronously with the first systolic movement of the heart, and a similar downward pull on the stopped heart causes a negative pressure wave in the aorta. Furthermore, the intraventricular pressure was found to rise at the point where the negative pressure wave began. The duration of the Anspannungszeit for the right ventricle estimated in this way (i.e. *c* to *f*) and also by the vibration *d* to *f* of the pulmonary artery curve are given in Table I.

It is evident that, although the diastolic pressure in the pulmonary artery is much lower than in the aorta, the Anspannungszeit is not materially different from that in the left ventricle.

TABLE I

Experiment	*Wave*	*Wave*
	(c – f)	(d – f)
C1, VI	.0292	.0195
C20, IV	.0280	.01875
C24, II	.0343	.0196
C25, V	.02808	.01872
C37, IIIa	.0384	.0192

Following the preliminary vibrations and the opening of the semilunar valves, the pressure rises suddenly to *g* and rapidly falls to *h* (Fig. 4). Since the vibration period of the primary pressure wave of *g* equals about .03 seconds and the inherent period of the instrument was .00636, it must evidently be attributed to a vibration of the blood column existing within the artery and not to an instrumental inertia. In all the records the amplitude of this vibration is much greater than in the systemic circuit. Following the primary wave the record assumes a rounded or flattened top which may be regarded as the true

systolic summit and then rapidly falls to the incisure. Calibrated records taken in four experiments indicate that the entire pressure range is included, on an average between 10 to 27 mm.

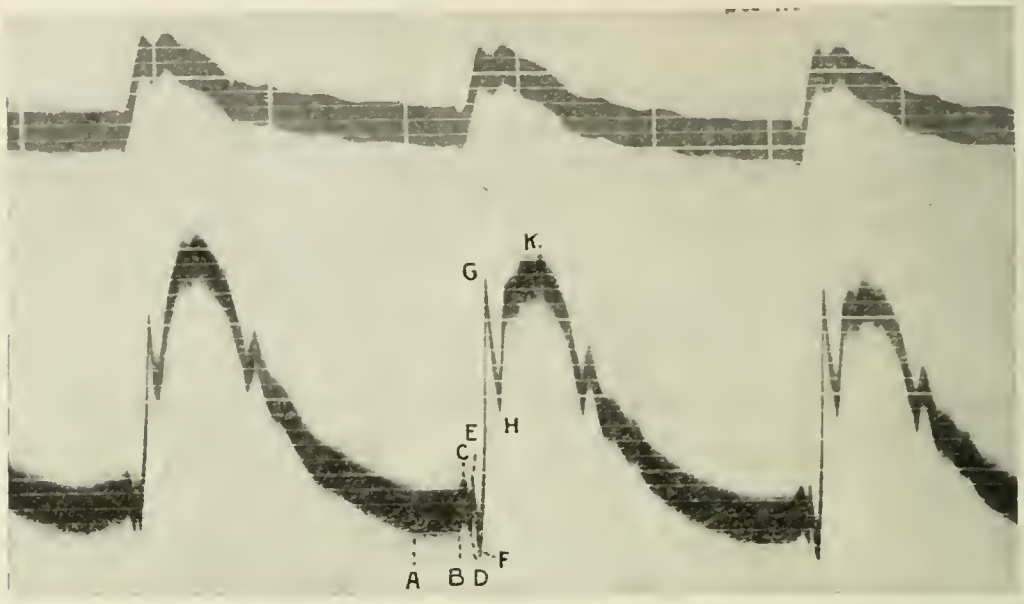

FIGURE 4. Three waves of normal pulmonary arterial pressure during natural respiration (lower record). First wave during expiration, second and third waves during inspiration compared with carotid pressure (upper record).

of mercury, giving a pulse pressure somewhat lower than the average found in the previous communication.

Influence of natural respiration. — An examination of the records of six experiments in naturally breathing animals reveals important changes, not only in the height, but also in the details of contour which are independent of heart rate changes. Their essential character is shown in the consecutive waves of Fig. 4, the first of which occurs during expiration and the last two during inspiration. Inspiration at its beginning causes a descent of the diastolic portion of the second curve which is followed by a proportionate fall of systolic pressure (measured at the height of the rounded curve) so that the pulse pressure is not greatly reduced. In the third wave, however, occurring at the height of inspiration, the systolic pressure is markedly lower and the pulse pressure is much reduced. Corresponding changes in the height of the carotid curve take place. The contour of the inspiratory pressure wave differs from that of expiration. In

the former the auricular wave is less prominent but the amplitude of the pulmonary vibration ($d - e - f$) becomes much greater. The time relations remain unchanged. The primary upstroke (gh) also becomes larger and sharper in its rebound and after its completion returns more rapidly to the top. The systolic summit (Fig. 4, k) which was smoothly rounded in expiration, approximates a short ascending or horizontal plateau which indicates a resistance more readily overcome.

Everything, in short, indicates a reduced tension or lowered elasticity coefficient of the vessels during inspiration, allowing

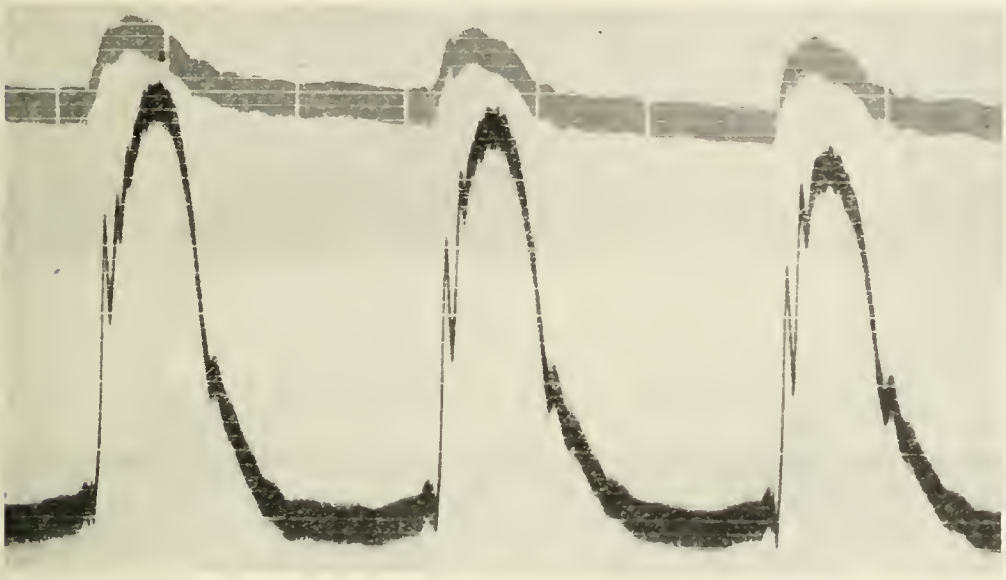

FIGURE 5. (Two thirds the original size.) Three waves of pulmonary arterial pressure after saline infusion (lower record). First, during expiration; second and third, during inspiration. Carotid pressure (upper record).

greater vibrations to take place. This is even more clearly shown in other records where two primary vibrations occur during inspiration and the second is damped out during the expiratory phase (Fig. 5).

Influence of saline infusion. — In the experiments above described the right auricular pressure during expiration was slightly above intrathoracic. In experiment *C*20, IV, e.g., from which the waves of Fig. 4 were taken, the right auricular pressure was 14 mm. of water during expiration and — 15 mm. during inspiration, pressures which may be regarded normal, inasmuch as they agree favorably with pressures found in un-

aesthetized animals.[1] In order to study the nature of the pressure changes when the right auricular pressure was beyond doubt above that which has been designated as "the critical level" by Henderson,[2] the influence of saline infusion was studied. The right auricular pressure rose to 68 mm. during inspiration while the intrathoracic pressure was 80 mm. A record taken immediately after this observation is shown in Fig. 5. These records show a pronounced increase in amplitude but otherwise the essential features are unaltered. Inspiration causes the same reduction in pressure amplitude although the change in systolic pressure is more pronounced. It is quite evident that, even when the venous pressure is above the critical value, the movements of respiration can modify the pressure in the pulmonary artery independently of cardiac rhythm.

Influence of lung inflation. — The effect of rhythmic artificial expansion of the lungs is shown in Fig. 6. The experiments

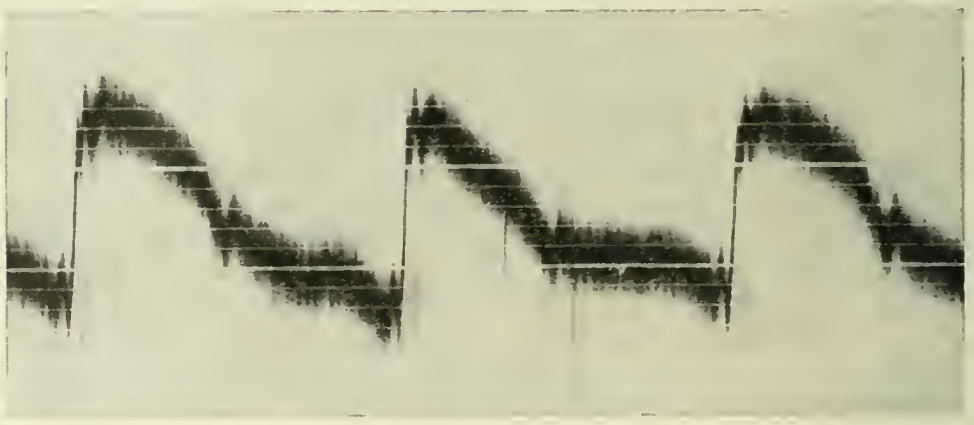

FIGURE 6. Effect of inflated lung (second wave) as compared with collapsed lung (first and third waves) on the contour and amplitude of curves.

were carried out with the chest open but the heart retained in the pericardium. The right auricular pressure measured 48 mm. of water. The records show that when artificial respiration was discontinued temporarily and the lungs collapsed, each wave reproduces the contour and height of the other. During mild expansion of the lungs, however, which in this experiment came every second beat, the shape during inflation is changed so that

[1] Data to be subsequently reported.

[2] HENDERSON and BARRINGER: This journal, 1913, xxxi, p. 352.

the systolic summit becomes pointed instead of rounded while the descent is more rapid. The "incisure" is low and the amplitude of the curve is reduced during inflation.

The conclusion may be drawn that when the systolic output and heart rate are constant, the state of lung expansion is capable of modifying the pressure curve in the pulmonary artery and is possibly in part responsible for the decreased systolic pressure and reduction of pulse pressure during natural inspiration.

Influence of the force of the heart. — The effect of the quantity as well as the velocity of ejection may be studied by

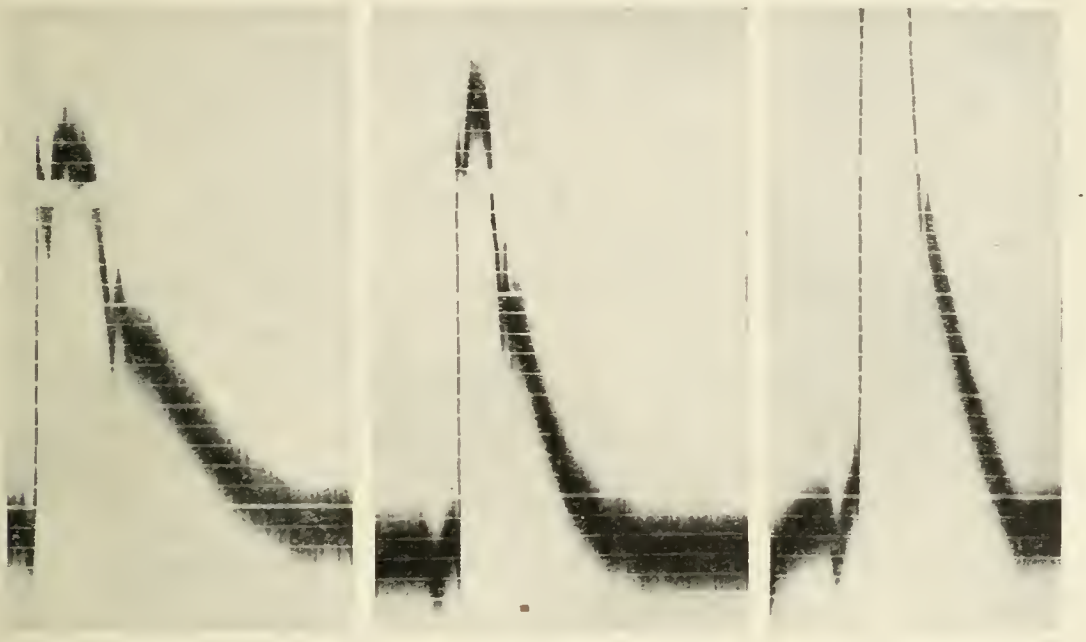

FIGURE 7. Three waves showing the effect of asphyxia of different degrees on the contour of pulmonary arterial waves.

the different stages in asphyxia or by the injection of adrenalin. In Fig. 7 are shown three waves taken from tracings at different stages of asphyxia. All were taken with open chest, in fact from the same experiment as the waves illustrating Fig. 6. The first of these simulates closely the normal tracings taken from the closed chest. The last two are characterized by a more rapid and pronounced primary rise and a conversion from a rounded top to a sharp peak. It also becomes evident that the vibration period of the primary wave and "incisure" decreases progres-

sively, the figures for the curves shown in Fig. 7 being respectively .03328, .0192 and .01024 seconds. This, obviously, is due to a changing tension of the vascular walls due to an increased filling or an active vascular constriction incident to asphyxia.

IV. Summary

A new optical manometer of great sensitiveness and high vibration frequency, adapted for studying the pressure variations within the pulmonary artery in "open" as well as "closed" chest experiments is described.

The pressure changes in the pulmonary artery, so recorded, exhibit essentially the detailed pressure oscillations that Frank has described in the systemic aorta. Measurements indicate that the "Anspannungszeit" of the right ventricle varies from .0280 to .0384 seconds. The pressure variations in calibrated records average from 10 to 27 mm. of mercury.

Natural inspiration changes the contour of the pressure curve by reducing the amplitude of the entire pressure wave but by increasing the amplitude and clearness of all short vibrations. The influence of natural inspiration persists when the right auricular pressure is elevated by saline infusion far above a critical pressure. Artificial inflation of the lungs in open chest experiments also reduces the amplitude of the pressure curve and causes a less rounded systolic summit. As this occurs when cardiac rate and output are probably unaffected, it may be concluded that lung inflation, itself, whether artificial or natural, can modify the contour and size of the pressure curves.

The size and shape of the pressure curves are appreciably modified by the variations in the force of the heart as well as by the condition of filling (and tonus?) of the pulmonary vessels as revealed during asphyxia.

OBSERVATIONS ON THE "EFFECTIVE" PRESSURE IN THE RIGHT AND LEFT AURICLES

By CARL J. WIGGERS

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I. The Critical Pressures for Ventricular Filling

THE term "effective pressure" has been aptly applied by Henderson and Barringer[1] to the difference between intrathoracic and intra-auricular pressures (measured, to be exact, at the auriculo-ventricular valves immediately before ventricular diastole). That this represents the actual pressure brought into play in ventricular filling seems plausible because, as may be inferred from experiments on a recently stopped heart, the intraventricular pressure at the beginning of diastole probably nearly approximates the intrathoracic pressure. To these authors also belongs the credit of having shown that when this "effective pressure" is great enough, i.e., becomes "critical," the heart acts in a uniform manner, so that the volume curves of the ventricles become "superimposable." In an earlier communication Henderson[2] pointed out that the effective venous pressures could not be considered "critical" unless they equalled at least 3 mm. of mercury, while, in a recent communication with Barringer, 50 mm. of water is regarded as a critical level. A re-study of many normal volume records taken in connection with another research[3] confirm, in the main, the observations of Henderson and Barringer, but indicate that a higher pressure than they report should be regarded as "critical" for the heart.

Without launching into details, the results showed that as the venous pressure increased up to 40 or 75 mm. of water, the

[1] Henderson and Barringer: This journal, 1913, xxxi, p. 288 and p. 352.

[2] Henderson: This journal, 1909, xxiii, p. 350.

[3] Wiggers: Archives of internal medicine, 1910, vi, p. 281.

active diastolic filling became more rapid and complete, thus augmenting the systolic discharge. The volume curves above this pressure were not entirely superimposable, however, until a venous pressure approximating or exceeding 150 mm. of water had been established.

In short, there exists a venous pressure level (40–70 mm. of water) that may be regarded as *relatively critical* in the sense that below such a level the efficiency of the heart is markedly influenced by venous pressure changes, while above it, also modified but to a slighter degree. On the other hand, there exists an *absolutely critical pressure* (approximately 150 mm. of water) above which systolic discharge is not improved and the beats become superimposable. These pressure levels, which may be designated "relatively and absolutely critical," were not constant in different animals nor under different conditions in the same animals, but varied, among other factors, with the size and tonus of the heart.

Since this was the case, it was deemed scarcely profitable to pursue further oncometer studies in relation to this point, for no light could thus be thrown on the relatively and absolutely critical pressures of the heart within the closed chest.

II. The Effective Pressure in the Right Auricle of the Unanaesthetized Dog

Before the assumption can be safely made that the heart in the closed chest follows the rule of "superimposability," it remains to establish definitely that the pressures are really above the critical value during all respiratory phases. The data upon this question are, however, insufficient. Venous pressure measurements in man are not conclusive since, aside from the relatively crude methods that necessity forces us to employ, and the absence of intrathoracic pressure measurements in each case, we have no evidence as to what venous pressures may be regarded "critical" for the human heart. In the case of experimental animals it is well recognized that such pressures as may be safely regarded "critical" for the dog's heart are not often encountered, but the question has not been definitely deter-

mined whether these lower pressures may not be the result of operation and anaesthetic as Henderson maintains. For these reasons, a comparative study of the intra-auricular and intrathoracic pressures in locally anaesthetized dogs was undertaken.

Methods. — In experimenting upon this question it is obviously necessary that augmented breathing from painful stimuli or psychical influence should not occur, otherwise the experiments would be objectionable on the same grounds as those on anaesthetized animals. By kindness and petting, dogs of a quiet nature can be made to rest calmly on an animal board and will breathe naturally. Under local anaesthesia an incision is made with a sharp knife through the skin and subcutaneous tissue across the path of the external jugular vein, which is quickly exposed and dissected free. A cardiac sound is introduced into the ventricle through the vein and then withdrawn so as to lie just on the auricular side of the tricuspid valves. It is then connected by fluid transmission to a damped water manometer or calibrated membrane manometer. The pressure variations are quickly read. The intrathoracic pressure is then recorded by a trochar inserted through an intercostal space well into the centre of the chest. After several deep breaths natural breathing is usually restored. The pressures within the thorax and right auricle are then read again.

Results. — The data shown in Table I indicate (1) that the right auricular pressure is generally slightly negative during inspiration, but becomes positive during expiration; (2) that the effective venous pressure is higher than is commonly supposed during all phases of respiration, and certainly higher than exists in animals with their chests open; (3) that the effective venous pressure is usually higher in inspiration than expiration, 63.1 mm. in the former and 43.6 mm. in the latter.

Are these pressures critical so that the volumes of both ventricles during inspiration and expiration are superimposable and the movements of respiration themselves without effect on the cardiac discharge and consequently on blood pressure? They are obviously less than those found absolutely critical in oncometer experiments by the writer, but this does not necessarily imply that they are not critical for the heart in the

unopened chest. If, however, the arterial pressure record in such animals were to show no indication of respiratory waves when cardiac rhythm is regular, the conclusion could be drawn that those pressures were critical. In two atropinized dogs, however, whose carotids were prepared under local anaesthesia, the arterial pressure *fell* during inspiration and *rose* during expiration, which is the rule in such cases. Since similar results

TABLE I

	Right auricular pressure		Intrathoracic pressure		Effective pressure	
Exp.	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.
C14	0	+ 7½	− 66	− 27	66	34.5
C15	0	+ 3	− 43	− 22	43	25
	+ 3	+ 10			46	32
C17	0	+ 5.8	− 80	− 40	80	45.8
C18	− 10	+ 0	− 34	− 20	44	20
C19	− 4	+ 46	− 82	− 12	78	58
C20	− 4	+ 10	− 60	− 44	56	54
C22	− 6	+ 26			?	?
C24	− 34	0	− 98	− 78	64	78
C25	− 10	6	− 78	− 50	68	56
C27	− 4	+ 20	− 90	− 13	86	33
				Average	63.1	43.6

All figures in mm. of water

(Fig. 3) have been obtained in anaesthetized animals whose auricular pressures were much higher, it may be concluded *that the effective auricular pressures in unanaesthetized dogs are below the critical level of the heart in naturally breathing animals.*

Certain objections to drawing such a conclusion upon this evidence must, however, be met. It may be asserted that slight variations of arterial pressure, due to rhythmic vasomotor changes or to mechanical variations of intra-abdomina

pressure, are possible even when the beats of the heart are superimposable. The first possibility may be met by the facts (1) that no proof exists that vasomotor variations of such short duration can occur or that they can react within so short a latent interval as must be assumed; and (2) that no proof exists that the rate and intensity of vasomotor discharges are related to the rate and depth of respiratory movements. Such an assumption, however, would be necessary to explain the exact correspondence in time and depth of respiration and blood pressure. Were the second possibility a factor we should expect the arterial pressure to rise during inspiration and not fall as is the case.

III. A Comparison of the Effective Pressures in the Right and Left Auricles

A determination of the relation existing between the effective pressures in the right and left auricles is important for many different reasons. The filling of the left ventricle is obviously determined by the effective left auricular pressure, and there are at present no data to warrant the assumption that the same pressure can be regarded as critical for both ventricles. Is it possible that the effective pressure of the left auricle may be above a critical level while that in the right auricle is below, or *vice versa?* Does a critical pressure in the right auricle imply an equally efficient pressure in the left auricle? Do the effective pressures of the two auricles rise and fall together with respiratory phases? Do the many influences which modify right auricular pressure also influence the left, to a similar extent, in a similar way? This communication in no sense purposes an extensive study of this many-phased subject, only enough observations bearing upon this problem are attempted to throw light upon those questions of cardiac behavior which demanded analysis before further progress upon the subject of the pulmonary circulation or the pathological physiology of hemorrhage could be made.

Methods. — The right auricular pressure of anaesthetized animals was obtained by a sound as before described. The reg-

istration of left auricular pressure involved opening of the thorax with its subsequent repair and a re-establishment of the original negative pressure. A large canula (6 mm. in diameter, 10 cm. long), guarded by a stop cock, was inserted directly into the left auricular appendage of the exposed heart to the level of the mitral valves, and tied. During the first experiments the

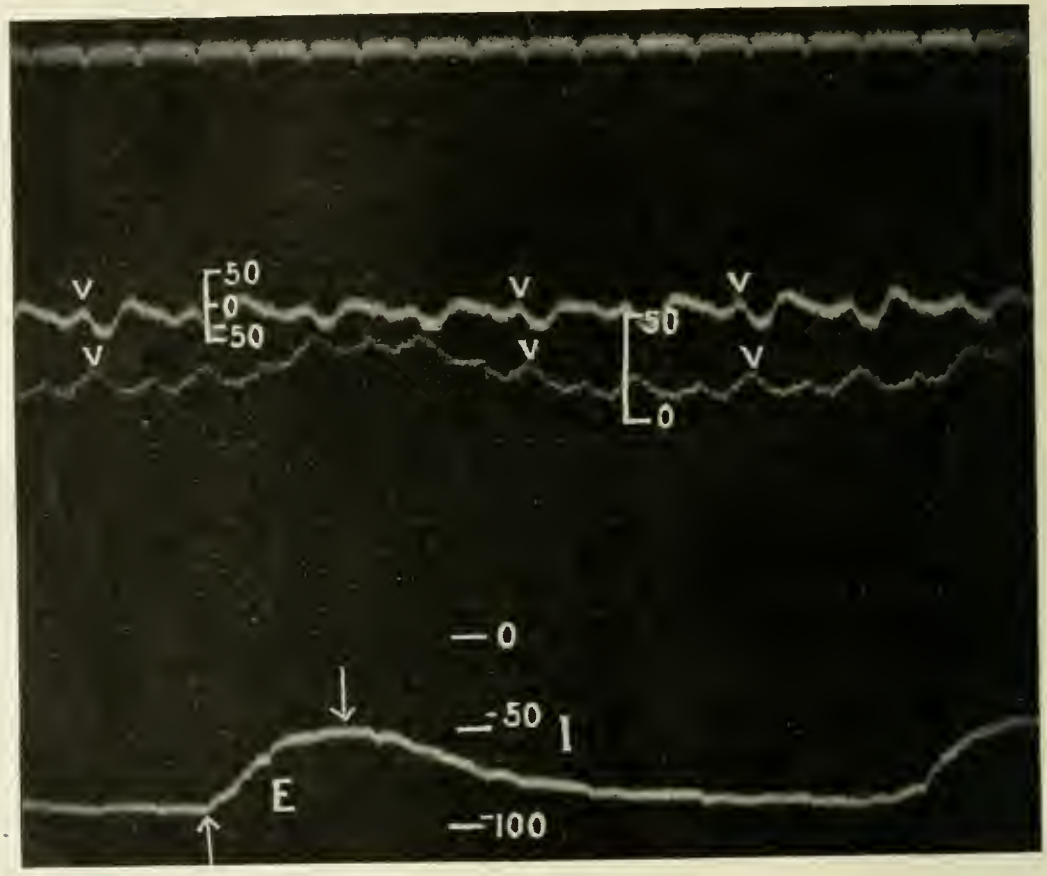

FIGURE 1. Pressures in auricles (upper record right, middle record left auricle) showing respiratory and cardiac variations. Letter V indicates points where pressures were measured.

stop cock was situated near the auricle and, after repair of the chest, was operated by a handle projecting externally. In later experiments it was found that coagulation could still be avoided when the stop cock of the canula was placed entirely without the chest. The right auricular sound and left auricular canula were connected with membrane manometers of special construction, purposely chosen of such sensitiveness that they responded to respiratory variations of pressure, but reacted only slightly to the cardiac variations. Their movements in the later experi-

ments were photographed on a moving bromide film. The entire manometer system (including sound and canula) had a vibration rate of 18–20 per second which, though low, was ample to study respiratory variations of pressure under ordinary conditions.

A flanged metal canula, with the inner lumen so guarded by a wire frame that occlusion by a lobe of lung was impossible, was screwed into the anterior chest wall and connected with a calibrated tambour for registration of intrapleural pressures.

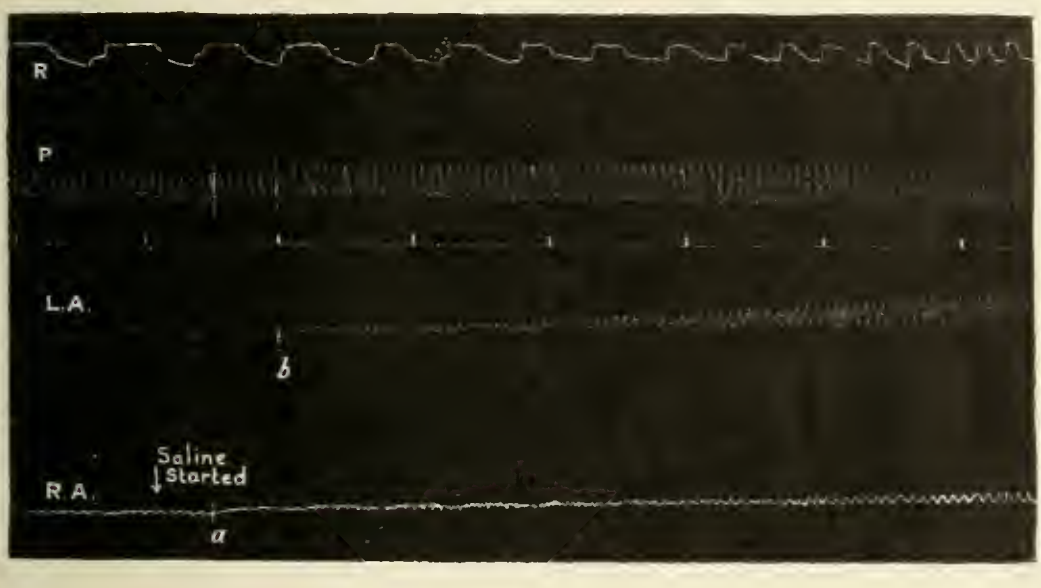

FIGURE 2. Effect of Saline Infusion: — R, respiration; P, pulse pressure with Hürthle spring manometer; LA, left auricular pressure; RA, right auricular pressure: *a* and *b* show where pressure began to rise in each auricle. Respiratory waves of auricular pressure which were present before perfusion disappear after perfusion has continued.

The chest was then surgically repaired, negative pressure restored, and the animal allowed to breathe naturally through a tracheal tube 30 cm. long. Special precautions were taken to locate exactly the end of the auricular canulas after each experiment and so establish the zero level.

The Absolute Pressure Relations between Left and Right Auricles. — The nature of the records is shown in Fig. 1. They display not only variations of pressure synchronous with respiration but, in reduced amplitude, those due to cardiac action. Since, under certain conditions to be analyzed later, the cardiac variations may even exceed in magnitude the respiratory changes (Fig. 2), it becomes necessary to select a definite point as a con-

stant place of measurement. Inasmuch as the ventricular filling is determined by the height of the pressure reached at the end of ventricular systole, it seemed logical to select for this point the beginning of the sudden fall of pressure at the end of ventricular systole (i.e., the third diastolic fall of Porter,[1] the third negative wave of Fredericq,[2] or the top of the v wave of Mackenzie.[3]

TABLE II

	Intrathoracic pressure		Right auricular pressure		Left auricular pressure		Effective pressure			
							Right auricular		Left auricular	
Exp.	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.
C_{16}	− 32	− 22	− 4	− 2	− 2	+ 8	28	20	30	30
C_{17}	− 80	− 40	− 5.8	0	− 10	+ 11	74.2	40	70	51
C_{18}	− 24	0	+ 55	+ 62	− 34	− 20	79	62	?	?
C_{19}	− 10	+ 28	− 4	+ 10	+ 2.4	+ 9.4	6	18	12.4	19.6
C_{20}	− 70	− 48	− 26	0	− 20	+ 20	44	48	50	68
C_{30}	− 44	− 17.5	+ 25	+ 50	0	+ 11.5	69	67.5	44	29
C_{31}	− 104	− 56	− 16.5	− 11	− 30	− 10	87.5	45	74	46
C_{32}	− 69.7	− 33	− 50	− 25	− 50	+ 6	19.7	8	19.7	39
C_{33}	− 87.8	− 50	+ 7	+ 7	++21	+ 38.5	94.8	57	108.8	88.5
						Average	55.8	40.6	51.1	46.4

All figures in mm. of water

The results are tabulated in Table II. A comparison of the effective right auricular pressures in these animals under general anaesthesia with those from animals under local anaesthesia (Table I) show that the average effective pressures (expressed in millimetres of water) of the former series (63.1 in inspiration

[1] Porter: Journal of physiology, 1892, xiii, p. 513.
[2] Fredericq: Zentralblatt für Physiologie, 1908, xxii, p. 297.
[3] Mackenzie: The study of the pulse, 1902, London.

and 43.6 in expiration) compare favorably with the average effective pressures in the latter (55.8 in inspiration and 40.6 in expiration). The difference in the effective pressures during inspiration and expiration was 15.2 mm. of water in the generally anaesthetized as compared with 19.5 mm. in the locally anaesthetized animals, a correspondence sufficiently close to warrant the conclusion that operative procedures, such as have been carried out in other experiments on the pulmonary circuit,[1] do not materially alter the auricular pressures after natural respiration has been re-established. In seven out of nine experiments the effective pressure was greater during inspiration than during expiration, the greatest variation being in experiment C 31, where it reached the exceptional figure of 42.5 mm. of water. In the two experiments, C 19 and C 20, where a reverse relation existed, the difference was slight.

The effective left auricular pressure averages 51.1 mm. of water during inspiration and 46.4 mm. during expiration. A comparison of these average figures with the average figures obtained simultaneously from the right auricle, as well as a comparison of individual experiments, indicate that, as a rule, the effective pressures of the two auricles are very nearly equal. An exception, however, is shown in several cases, one of which is published in Fig. 1.

Effect of Saline Infusion.—The effect of introducing warm saline solution rapidly into the external jugular vein was studied in six experiments. Infusion was usually continued to the point where cardiac irregularities, due to the enormous distention, occurred. A study of such records shows that the general level of the right auricular pressure began to rise immediately and after a latent period, varying from 2.25 to 3 seconds (i.e., an interval occupying four to six heart beats), the left auricular pressure also rose (Fig. 2). As infusion continued, the pressure curves of the two auricles continued to ascend, running practically a parallel course (Table III). This observation is, in itself, direct proof that the output of the right ventricle has been increased and that, therefore, the previously existing right auricular pressure was not sufficient to insure maximal efficiency of heart action.

[1] Wiggers: This journal, 1912, xxx, p. 233, and 1914, xxxiii, p. 1.

In three experiments the rate and depth of respiration remained unchanged during infusion and the cardiac waves of the venous pulse were not materially increased in size. A perusal of one of these records, shown in Fig. 2, indicates that, after a

TABLE III

EFFECT OF SALINE INFUSION ON EFFECTIVE PRESSURE

EXPERIMENT C18X

Observation	Right auricular pressure	Left auricular pressure	Intrathoracic pressure	Effective pressure		Carotid pressure	
	Exp.	Exp.	Exp.	Right auricle	Left auricle	Insp.	Exp.
1	+ 66	− 20	− 34	100	14	Fell	Rose
2	+ 70	+ 20	− 32	102	52	"	"
3	+ 80	+ 42	− 28	107	70	"	"
4	+ 110	+ 80	− 33	143	113	"	"
5	+ 130	+ 100	− 25	155	125	None; returned upon deeper breathing	
EXPERIMENT C19							
1	+ 40	+ 20	− 12	52	32	Fell	Rose
2	+ 46	+ 24	− 12	58	36	"	"
3	+ 60	+ 56	− 12	72	68	"	"
4	+ 80	+ 88	− 12	92	100	"	slightly

pronounced infusion has taken place, the respiratory variations are obliterated. Since changes of intrathoracic pressure still occur, the effective pressure must vary more than normally during inspiration and expiration. A quantitative analysis of these records by application of the calibration scale indicates that this is indeed the case (Tables III and IV).

How high a left auricular pressure is necessary in order that the discharge of the left ventricle is not influenced by respira-

tion? A determination of the effective auricular pressure at which the respiratory variations of carotid pressure are abolished may be used, as before, to determine this point. In one of the two previous experiments, in which carotid pressures were simultaneously recorded by a Hürthle spring manometer, it was found that the respiratory waves of carotid pressure were obliterated when the effective pressure in the right auricle equalled 155 mm.

TABLE IV

EXPERIMENT C10VI

Observation	Right auricle		Intrathoracic pressure		Effective right auriular pressure		Carotid pressure	
	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.	Insp.	Exp.
1	− 20	− 13	− 60	− 28	40	15	Fell	Rose
2	− 13	+ 26	− 60	− 28	47	54	"	"
3	+ 36	+ 72	− 60	− 27	96	99	"	"
4	+ 91	+ 91	− 55	− 27	146	118	" (slightly)	" (slightly)
5	+ 162	+ 169	− 52	− 25	214	191	No change; irregular beats occasionally	
6	+ 260	+ 260	− 50	− 23	310	283	No change; many irregular beats	

of water and in the left auricle 125 mm. of water pressure, but, in this case, deep breathing re-established the respiratory waves.

To obviate the possible criticism that operative procedures had in some way modified the heart action so as to change the critical pressure level in these cases, two experiments were carried out in which the carotid pressure was photographically recorded by Frank's spiegelmanometer and the right auricular pressures by an optically recording manometer. Intrathoracic pressure changes were recorded by a calibrated Frank's capsule covered with heavy rubber. The results of experiment C 10 VI are shown in Table IV. They indicate an entire abolition of respiratory pressure waves only when effective right auricular pressure during

expiration reaches the level 191. The end result of the other experiment is shown in Fig. 3. Here the effective pressure in the right auricle during inspiration was over 90 mm. of water, but respiratory variations in carotid pressure continued unaltered.

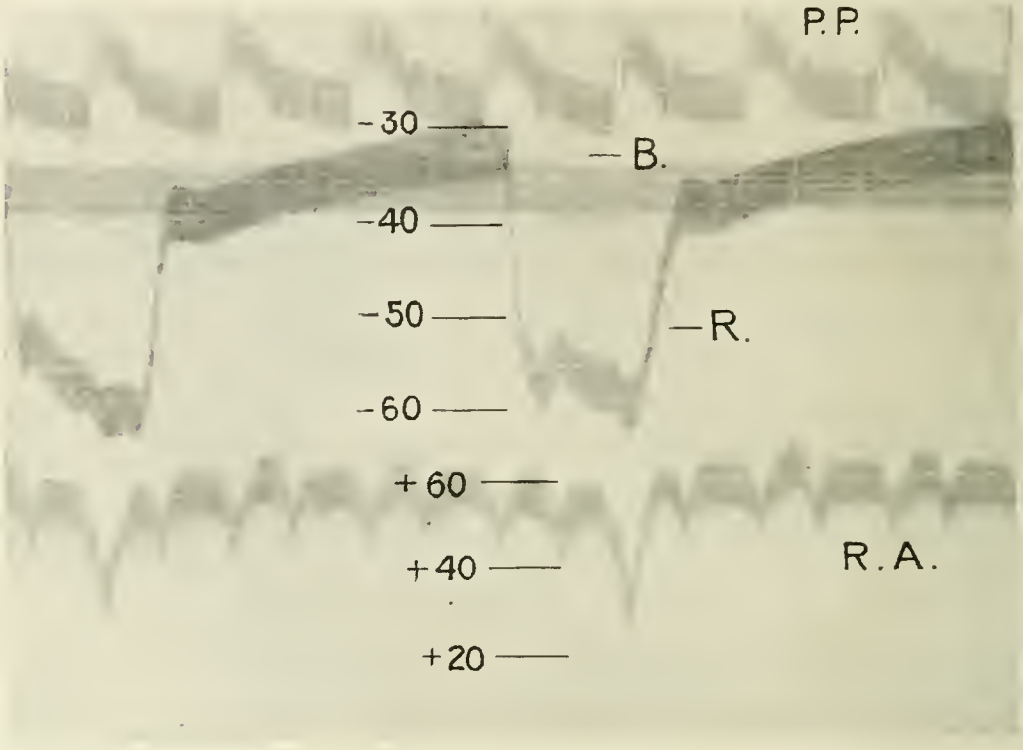

FIGURE 3. Showing inspiratory fall of systolic and diastolic arterial pressures continuing after marked saline infusion. PP, carotid pressure with Frank's spiegel manometer; B, base line; R, intrathoracic pressure changes recorded by Frank's capsule, downstroke in inspiration; RA, right auricular pressure with optical manometer.

One of two conclusions must be drawn. Either a left auricular pressure much higher than suggested by Henderson and Barringer is critical for the left ventricle within the unopened chest, or the auricular pressure does not solely determine the systolic discharge when the forces of respiration are acting.

THE SECRETION OF THE GASTRIC JUICE DURING PARATHYROID TETANY

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I. Introduction

CARLSON[1] in his studies on the conditions of the digestive tract in parathyroid tetany found that even in severe tetany the digestive movements of the stomach and the intestines may be quite normal, and that the deviation from the normal is in the direction of depression. In spite of this immunity of the motor apparatus to the "tetany toxins," there was a long delay of the food in the stomach. Normally eight and one-half hours were required to empty the stomach after feeding the test meal, but after parathyroidectomy this time was increased to eighteen and three-fourth hours. The object of the present work was to determine the cause of this delay, whether it was due either to changes in the rate of secretion, or the character of the juice, or both.

II. Experimental Methods

1. General Plan. — Animals with Pawlow accessory stomachs were fed a test meal consisting of 25 grams of lean raw beef, into which 2 grams of Witte's peptone had been thoroughly worked. The beef was freed from the obvious fat and connective tissue, and ground through a meat chopper three times. The gastric juice was then collected, estimations being made of quantity, digestive activity, titratable acidity, and the active secretion period. Having determined the normal for a given animal, the whole thyroid-parathyroid apparatus was removed.

[1] Carlson: This journal, 1912, xxx, p. 309.

The test meal was then fed at intervals until death or recovery, and the changes in the juice noted. In one case, cat no. 19, a partially successful transplant of the parathyroid gland into the peritoneum was obtained.

After the removal of the glands the animal would often eat quite normally on the day following and then refuse food the second meal. In other cases the animals refused to eat even the first meal. It was then necessary to feed forcibly. The peptone had been added with the idea that in such conditions an abundance of secretogues would be present to overcome a possible depression in psychic secretion. In giving the meal it was rarely necessary to do more than put the food in the mouth of the animal, who chewed and swallowed as usual.

In order to gain an idea of the effects of the ether and traumatism on the gastric secretion, control operations were performed on nine animals. In these cases the technique was the same as in the removal of the glands, care being taken to isolate the blood supply.

Ten days were allowed to elapse following the stomach operation before test meals were fed. After this time a uniform experiment could be obtained. In general the animals numbering from 16 to 30 were kept under observation for periods of time ranging from one and one-half to three months. In this way it was known that we were dealing with normal cats.

Cats are ideal for work of this type. They rarely tear off the bandages, and the primary union of the mucosa to the skin can be maintained, if they are watched so that the drainage tubes do not get out of the stomach pouch. They keep in good condition, many of them increasing in weight after the stomach operation; and on the whole they bear confinement well, if the cages are kept thoroughly clean. Vomiting, which is such a pronounced symptom of parathyroid tetany in dogs, is practically absent.

(2) **The Operation.** — Since the only extended work on stomach secretion, in which cats have been used, is that reported by Riasantseu[1] in 1895, who investigated the psychic secretion in animals with fistulæ of the stomach and oesophagus, we may

[1] Riasantseu: Archives des sciences biologiques, 1895, iii, p. 216.

note the modifications of the technique of the Pawlow[1] operation that proved serviceable in our work.

(*a*) The animal was fasted 24 hours to insure an empty stomach.

(*b*) A subcutaneous injection of atropine hydrochloride (0.05 mg. per kilo body weight) was given one-half hour preceding the administration of the anaesthetic, in order to dry up the extensive and troublesome mucous secretions.

(*c*) After relaxation under the anaesthetic, 50 c.c. of physiological salt solution was introduced into the stomach with a tube. This was afterwards drawn out by means of a sterile pipette through a nick in the anterior wall of the stomach, along the line of the future incision. The salt solution serves to wash out the stomach debris and dilate the walls, so that a better notion is obtained of the size of the sac that is being isolated.

(*d*) Pawlow found that by making the partition between the two stomachs of flaps of the mucosa, dissected back from the incision across the isthmus, he was able to prevent secondary communications from developing. In meeting this difficulty, it was found unnecessary to do any extensive dissecting, providing the lines of sutures were placed so as not to fall over each other. In closing the large stomach, two lines were run, beginning at either end of the cuts through the anterior and posterior surfaces, and meeting in the midline. In the case of the small stomach, the sewing was begun in the middle of the isthmus, joining the anterior and posterior surfaces.

(*e*) To protect the healing abdominal surface from the secretions, a rubber drain tube was sewed into the opening of the small stomach. This was removed when active feeding was begun.

(*f*) Two hot water bottles were placed on either side of the animal during the operation to prevent loss of heat, and shock.

(*g*) Water was given after 24 hours, and feeding with 15 c.c. of milk at a time was begun 3 to 4 days following the operation.

3. Collection of Juice. — Since the periods during which the juice was collected were long, and in all the details of the work an attempt was made to disturb as little as possible the

[1] Pawlow: Work of the digestive glands, London, 1910.

normal habits of the animal, no collecting frames or holders were used during the experiment. Unless hungry, a cat lies coiled up in a ball, sleeping most of the time. In such a position there is no difficulty experienced in collecting the juice, but just in the middle of an important experiment the animal may find it more comfortable to lie on his back or in some other equally impossible position for collecting the juice. Many unsuccessful attempts were made to prevent loss of juice before adopting the type of collecting tube shown in Fig. 1. It consisted of a long, narrow neck *c* and an expanded bulb *d*. When the animal was lying on the side, the fluid drained into the bulb. If he turned over on his back, then the juice plugged the opening and prevented the entrance of the air. About the only source of loss came from an occasional damming back of the juice in the region of *a*, and absorption by the bandage. This could be remedied by placing the hole *b*, through which the juice was drawn off, lower down. Collections from the container were made at one to two hour intervals depending on the rate of secretion.

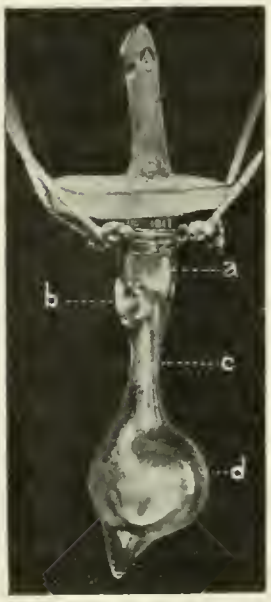

FIGURE 1. Device for collecting the juice from the Pawlow stomach pouch in cats Explanation in text.

4. Acidity. — The free and total acidities were obtained by titration, using dimethyl-amino-azo-benzene and phenolphthalein as indicators. In the case of cats 2 to 14, 1 c.c. of the sodium hydroxide used was equivalent to 1.67 mg. of HCl; in the remaining cases 1 c.c. was equivalent to 0.977 mg. of HCl. The latter strength was quite satisfactory since it required 3.5 to 5.5 cc. of the alkali to neutralize 1 c.c. of the juice.

5. Digestive Activity. — Since the quantities of the juices available were small and the number of determinations to be made large, none of the more recent methods based on the addition of varying concentrations of enzyme to a fixed quantity of substrate could be used. The method finally adopted consisted in taking the time required by 1 c.c. of juice to digest 10 mg. of dry ox fibrin. The fibrin was washed, boiled, and

preserved in alcohol. It was then shredded, cut into small pieces of approximately the same size, and dried in a vacuum desiccator. All the determinations were run on the same sample of fibrin. The end point is necessarily an arbitary one for the individual, for there are all variations in the size of the particles before the complete solution of the fibrin. In juices which will digest the 10 mg. in 1 to 3 hours the end point can be read within a range of 15 minutes; but for juices requiring 7 to 8 hours the limit is more often 30 minutes. In many of the samples mucus was present in large quantities, especially towards the end of the digestive period or during tetany. In such cases the juice was centrifuged, if a sufficient sample was obtained; if not, a dilution with water was made and the mixture placed in an ice chest until the next day. The mucus was then found to be gathered into a small coherent ball, which did not interfere with the determination of the fibrin solution.

6. Active Secretion Period. — In order to secure the end point of the active secretion period, the conditions of the juice during fasting must be observed. It would naturally be thought that the disappearance of free acid from the juice would serve as a criterion, but some animals seem to have a certain amount of acid present long after their stomachs are empty. Again, the quantity of the fasting secretion may be considerable, though it usually is insignificant. The presence of mucus in appreciable quantities occurs at the end of digestion. The end point of the active secretion was therefore considered to be reached when the acidity and quantity corresponded to that of the fasting stomach, and mucus made its appearance.

III. Results

1. Examination of the General Summary Table. — In order to summarize the observations so that they may be grasped readily, the juices collected during the active normal secretion period are compared with those obtained during the same length of time after removal of the glands. This period, as can be seen from Table I, in normal animals varies from 5 to 8 hours. In the larger number of cases the end point lies between the

TABLE I

General Summary of the Changes in the Secretion of Gastric Juice in Parathyroid Tetany

Number of animal	Quantity of juice in c.c.		Free acidity in percentage of HCl		Total acidity in percentage of HCl		Digestive activity in hrs.		Active secretion period in hrs.	
	Normal	Tetany	Normal	Tetany	Normal	Tetany	Normal	Tetany	Normal	Tetany
2	4.77 [3]	5.09 [6]	0.358 [3]	0.332 [6]	0.534 [3]	0.417 [7]	2.8 [4]	3.5 [3]	5.6 [3]	15.4 [7]
3	4.41 [3]	0.70 [3]	0.183 [3]	0.070 [2]	0.417 [3]	0.317 [2]	2.6 [3]	2.2 (*a*)	7.0 [3]	12.0 (*b*)
7	4.84 [8]	2.19 [1]	0.367 [10]	0.066 [1]	0.517 [5]	0.501 [2]	1.9 [10]		6.1 [10]	(*c*)
9	1.52 [6]	1.03 [3]	0.201 [7]	0.210 [2]	0.484 [5]	0.384 [2]			5.1 [6]	11.0 [3]
11	8.21 [7]	4.70 [2]	0.216 [7]	0.203 [2]	0.434 [7]	0.434 [2]	2.1 [7]	3.0 [2] (*d*)	6.6 [7]	10.0 [2]
13	7.37 [4]	0.20 [1]	0.342 [4]		0.450 [4]		1.7 [4]		8.1 [3]	(*c*)
14	5.41 [3]	6.95 [2]	0.282 [3]	0.186 [2]	0.467 [3]	0.334 [2]	2.8 [2]	2.8 [2] (*d*)	7.2 [3]	13.0 [1]
17	5.70 [12]	6.56 [5]	0.439 [15]	0.361 [5]	0.488 [16]	0.449 [5]	3.2 [11]	4.5 [5]	8.0 [16]	16.0 [4]
18	14.10 [12]	3.68 [1]	0.459 [16]	0.166 [1]	0.527 [16]	0.293 [1]	2.9 [8]	7.0 [1]	7.2 [13]	(*c*)
20	7.87 [10]	6.88 [4]	0.429 [10]	0.381 [4]	0.488 [9]	0.439 [4]	2.6 [9]	4.8 [5]	7.4 [10]	14.6 [4]
21	5.98 [7]	5.58 [4]	0.449 [6]	0.390 [4]	0.527 [6]	0.468 [4]	3.0 [6]	3.8 [4]	7.6 [5]	19.0 [4]
22	5.52 [9]	4.82 [9]	0.322 [9]	0.332 [8]	0.381 [10]	0.439 [8]	4.0 [8]	5.7 [8]	6.3 [12]	15.5 [7]
23	9.56 [8]	8.65 [3]	0.283 [9]	0.205 [2]	0.361 [10]	0.283 [3]	3.6 [9]	6.4 [3]	6.3 [10]	21.0 [2]

24	12.89 [8]	6.07 [2]	0.283 [9]	0.234 [2]	0.361 [9]	0.322 [2]	3.8 [8]	6.5 [2]	6.9 [10]	26.0 [2]
25	12.98 [11]	8.66 [9]	0.332 [11]	0.224 [9]	0.390 [11]	0.293 [9]	3.4 [10]	6.6 [9]	6.9 [11]	13.0 [6]
26	11.08 [11]	8.88 [4]	0.381 [9]	0.381 [9]	0.449 [11]	0.449 [4]	3.3 [11]	6.6 [4]	6.8 [11]	16.0 [3]
27	10.11 [10]	8.21 [9]	0.302 [10]	0.117 [9]	0.390 [10]	0.224	3.7 [10]	13.8 (*e*) 4.6 [4] (*d*)	6.5 [10]	12.6 [8]
28	9.71 [8]	6.61 [3]	0.273 [9]	0.244 [3]	0.390 [11]	0.322 [3]	3.0 [10]	3.8 [3]	5.7 [11]	9.0 [2]
29	3.90 [5]	2.22 [7]	0.254 [5]	0.244 [6]	0.341 [5]	0.420 [6]	4.3 [5]	6.7 [5]	6.2 [5]	10.8 [5]
30	5.92 [4]	3.88 [8]	0.400 [5]	0.351 [8]	0.498 [5]	0.478 [8]	3.2 [5]	5.0 [8]	6.6 [5]	12.7 [9]

(*a*) Activity was zero on the second day, as no free acid was present.
(*b*) No end point could be secured the second day.
(*c*) Death before the first meal was finished.
(*d*) Pepsin determinations made by addition of acid to digest.
(*e*) For several days the amount of acid secreted was too small to cause appreciable digestion. In these cases the digestion period was arbitrarily fixed as 24 hr.

sixth and seventh hours. Hence the average active normal secretion period for the comparative studies was taken as 6 hours. The exponents to the figures indicate the number of observations for which this particular figure is an average.

In the case of cat no. 16, who survived the parathyroidectomy, the period following the removal of the glands is divided into two parts, one in which symptoms were present, and one in which they were absent.

Normal

Quantity, 3.9 c.c.; free acidity, 0.37 per cent; total acidity, 0.45 per cent; activity, 2.9 hrs.; active secretion period, 6.4 hrs. Number of experiments 20.

Symptoms

Quantity, 3.1 c.c.; free acidity, 0.29 per cent; total acidity, 0.42 per cent; activity, 5.8 hrs.; active secretion period 10.7 hrs. Number of experiments 5.

No Symptoms

Quantity, 4.7 c.c.; free acidity, 0.28 per cent; total acidity, 0.37 per cent; activity, 5.8 hrs.; active secretion period, 7.2 hrs. Number of experiments 11.

A partially successful transplant of the parathyroids into the peritoneum was obtained in the case of cat no. 19. For a few days the animal showed a mild grade tetany (designated "Insufficiency" period), which gradually cleared up ("Recovery" period). During this time the animal continued to lose weight, although it consumed large quantities of food. Finally the transplant was removed, giving rise to the "Extirpation" period. Histological examination of the transplant showed gradual absorption and replacement by granulation tissue.

Normal

Quantity, 7.42 c.c.; free acidity, 0.35 per cent; total acidity, 0.44 per cent; activity, 3.1 hrs.; active secretion period, 5.5 hrs.

Insufficiency

Quantity, 7.5 c.c.; free acidity, 0.30 per cent; total acidity, 0.38 per cent; activity, 3.7. hrs.; active secretion period, 10.1 hrs.

Recovery

Quantity, 8.4 c.c; free acidity, 0.35 per cent; total acidity, 0.45 per cent; activity, 3.5 hrs.; active secretion period, 7.5 hrs.

Extirpation

Quantity, 7.5 c.c.; free acid, 0.31 per cent; total acidity, 0.37 per cent; activity, 5.9 hrs.; active secretion period, 10.7 hrs.

An analysis of the table shows the following general facts.

(*a*) *Quantity of Juice.* — In two cases, 14 and 17, there was a slight increase in quantity of juice; in three others, 2, 19, and 21, there was practically no change; while all the others showed varying degrees of depression ranging from a small amount to almost total suppression of the secretion.

(*b*) *Free Acidity.* — In no case was there an actual increase in the free acid. In cases 2, 9, 11, 19 (during recovery), 22, and 26 the change (0.02 per cent) was so slight that it can be looked upon as coming within the normal variation. In the other 16 cases there was depression.

(*c*) *Total Acidity.* — Cat no. 29 showed a slight increase in total acid, cats nos. 7, 11, and 26 showed no change; the others showed depression. Attention is called to the fact that in all cases the variations of the acidities is in the line of depression, though this is not clearly shown in the table. This fact is masked in the averaging of the hourly determinations. The point can be made clear by taking a specific case. Suppose that the normal acidities at the end of the fifth hour drop to a value one-half that during the preceding hours; that after parathyroidectomy the hourly secretion is only a trifle lower than normal, but is continued say for 12 hours instead of 5; then it is seen that the average for the 6 hours may be equal to, or slightly higher than the same figures under normal conditions.

(*d*) *Activity.* — Number 3 showed a slight acceleration in digestive activity the first day after removal of glands; but on the second, as there was no free acid present, the activity fell to zero. This same juice made up with acid showed normal digestive power. An examination of the quantity secreted will show that we are not dealing with an active juice, but a mucous

discharge, which is high in pepsin. An interpretation of this will be considered later. In case of no. 14 the juices were all made up to a constant acidity, so we have an apparent increase in peptic activity. The remainder of the animals showed marked and striking depression varying from 26 to 400 per cent.

(*e*) *Active Secretion Period.* — The normal active secretion period is slightly shorter than Carlson[1] found for the complete emptying of the stomach after the same test meal. This may be explained by the addition of bismuth subnitrate to his meal, or perhaps by finer grinding of our meal, but more probably it means that traces of food may remain in the stomach without being able to furnish adequate stimuli for secretion. Perhaps both factors are concerned. The lengthening of the period in tetany is so obvious that it needs no comment.

2. Effect of Control Operations. — Control operations on nine animals showed, that the ether and surgical trauma had no significant effect on the secretion the day following. The quantities and acidities, both free and total, fluctuated about the averages of the normal runs, some slightly higher, some slightly lower, many the same. In the case of the activity the variations were in the direction of acceleration rather than depression. However, there was an average lengthening of the active secretion period from 6.5 to 7.9 hours.

As there is a fundamental agreement in the variations, some explanation other than the vagaries of chance ought to be sought for them. The increased activity of the juice coupled with the maintenance of the quantitative output means that the secretory mechanism is working at a little higher level than normal. The lengthening of the digestive period at first seems incompatible with a more efficient secretion. Obviously a motor deficiency may be the sufficient cause of the delay. This possibility is rendered improbable by the findings of Carlson, that even removal of the parathyroid glands leaves the motor mechanism practically normal until the last stages of tetany are reached. Attention has been previously called to the fact that traces of food may remain in the stomach without giving rise to secretion. This is supported by the experience of everyone

[1] Carlson: *ibid.*

who has attempted to wash clean the stomach of a dog fed 16 to 18 hours previously. Such pieces of food might easily stimulate an hyper-irritable mucosa through local reflexes, while they would not affect a normal one.

3. Is there a Depression in the Quantity of Acid Secretion?—Pawlow has contended that the acid cells secrete into the stomach a fluid with a fixed and definite hydrogen ion concentration, and that the variations in titration values obtained are functions of the rate of secretion and the available mucus. Hence the juice collected from a previously fasting stomach during the first hour of secretion will show a lower acidity than that collected during the second. Further, the acidity will continue to rise parallel to the rate until a juice is obtained which differs in H ion concentration from that secreted, only by the amount necessary to activate the pepsinogen. This view has been supported by Bickel,[1] Hoffmeister and Wintgren,[2] Umber,[3] and other workers. It is very difficult to establish whether we have in tetany a diminished H ion output or not. It is true that the pronounced diminution in the secretion of the glands, and the quantities of mucus present in many cases would furnish sufficient explanation of the lowering of the acidities. However, there is evidence also for the other view, that we are dealing with an actual lowering of H ion output.

In a few of the experiments the quantity of juice secreted per hour increased only slightly from the first, and yet the total acid rose higher and higher, reaching the maximum about 6 to 7 hours after the meal. Of course, one might assume that it required this length of time to wash the stomach free from mucus, but this is doubtful. In cat 18 the acid increased after the fourth hour from 0.175 to 0.527 per cent; the quantity of juice had been secreted at the rate of 0.53 c.c. per hour during the previous hours, but at the fifth it rose to a rate of 1 c.c. The quantity of juice was doubled approximately, while the acid was increased three times.

In general, since the quantity of juice suffered a depression,

[1] Bickel: Deutsche medizinische Wochenschrift, 1906, xxxii, p. 1323.

[2] Hoffmeister and Wintgren: Archiv für Hygiene, 1907, lxi, p. 187.

[3] Umber: Berliner klinische Wochenschrift, 1905, xlii, p. 56.

there were relatively few instances in which the secretion for 4 to 5 hours after the test meal was the same in quantity on a normal and a parathyroid day. The comparison of the total acidities under these conditions should be suggestive; but it would not constitute final evidence, for one could not rule out the possibility of slight increase in mucous secretion, which would neutralize the acid and at the same time give a false impression as to the quantitative output. On this point one can only offer the fact that the mucus if present was not there in such quantities as to be readily observable. Data from four cases are available on this point.

Cat Number 20. Normal Animal

December 26, the quantity of juice for four hours after test meal was 2.72 c.c.; total acidity, 0.51 per cent.

January 12, quantity, 3.9 c.c.; total acidity, 0.52 per cent.

Parathyroidectomized Animal

February 8, quantity, 4.7 c.c.; total acidity, 0.39 per cent.

Cat Number 23. Normal Animal

February 14, quantity, 5.6 c.c.; total acidity, 0.42 per cent.

February 26, quantity, 6.1 c.c.; total acidity, 0.46 per cent.

Parathyroidectomized Animal

March 13, parathyroidectomy was performed.

March 14, quantity, 9.7 c.c.; total acidity, 0.30 per cent.

March 17, quantity, 7 c.c.; total acidity, 0.37 per cent.

The cat died in tetany on March 17, 6 hours after feeding.

It will be noted that the quantities of juice were greater on the parathyroid days than on the normal ones, and yet the acid was lower. Further, attention is called to the acidity of the secretion just preceding death, which is higher than on the day following removal of glands.

Cat Number 25. Normal Animal

May 2, quantity, 7.6 c.c.; total acidity, 0.44 per cent.

Parathyroidectomized Animal

May 23, quantity, 7.4 c.c.; total acidity, 0.37 per cent.

May 28, quantity, 6.6. c.c.; acidity, 0.25 per cent.

Cat Number 27. Normal Animal

May 9, quantity, 9.15 c.c.; total acidity, 0.46 per cent.

May 17, quantity, 8.5 c.c.; total acidity, 0.42 per cent.

Parathyroidectomized Animal

May 23, quantity, 8.6 c.c.; total acidity, 0.31 per cent.

May 23, quantity, 9.4 c.c.; total acidity, 0.30 per cent. This represents two meals eaten by the animal on the same day.

Reference to Table I will show that in the cases of animals 2, 16, 17, and 19 the quantity of juice over the six hour period was not diminished, but the total acidities were somewhat lower than can be attributed either to experimental error or individual variation. From a consideration of these cases the evidence is very strong, if not conclusive, that we are dealing with an actual diminution of the H ion output.

4. Discussion of the Activity. — The digestive activity of any gastric juice is the resultant of the available H ion and the pepsin. It was considered that the mere dilution of the juice with water would give a good index of the efficiency of the juice as a digestive agent. Michaelis and Davidsohn[1] have shown that an accurate notion of the available H ion in various pathological conditions cannot be secured from titration. The titration may show only a slight variation from the normal, while the actual variation in H ion as measured by the hydrogen electrode may be 200 to 300 per cent. Hence, then, a juice of low activity with practically normal titration value might have a smaller amount of pepsin, or it might have its H ions bound in such a way as to be unavailable for driving the reaction. In order to determine which of these factors was involved, hydrochloric acid in many cases was added to make the concentration up to a definite quantity.

The curve of normal activity is usually a trifle lower in the first than the succeeding hours during which the food remains in the stomach. In many cases, however, it attained in the first hour the constant high level characteristic of the active secretion period. A second rise is found just at the close of secretion. This is simultaneous with a decrease in quantity of juice and the appearance of mucus. It is explained by the fact that there is a smaller amount of fluid to flush out the final

[1] Michaelis and Davidsohn: Zeitschrift für experimentelle Pathologie und Therapie, 1910–11, viii, p. 398.

pepsin formed, and is not to be regarded as in any sense an index of a more efficient secretion. Following this, the pepsin drops to the low level (6 to 7 hours) found in the fasting stomach. Attention is especially called to the rise at the end of active secretion, for this is significant of cells which are putting out pepsin at a normal rate and water in decreased quantities.

After the removal of the parathyroids, in the great majority of cases the activity immediately fell, often to one-half its former value. In cases 27, 28, and 30, where the onset of the symptoms was slow, we have a condition analogous to that found at the close of the normal secretion period; i.e. decrease in quantity of juice, but maintenance of activity at the same or slightly higher level. Normally cat 30 secreted over a period of 6 hours 5.92 c.c. of juice with an activity of 3.2 hours, but the day following the operation, she secreted over the same period 2.66 c.c. with an activity of 2.5 hours. On the days following, with slight increases in quantities of juice, the activity gradually fell to 3.4, 5, and 6.3 hours and maintained itself at these low levels as long as animal was under observation.

How are we to explain this lowering of activity? Is it due to lack of H ions or is there a decrease in quantity of pepsin? In order to answer the question tables were constructed for each animal, showing the titratable free acidity in the activity determinations made on the juices from the normal and the parathyroidectomized animals. In general such tables showed that the acidities of the activity determinations were well within the range which had been found to drive the reaction in the case of normal animals.

In case of cat no. 25, forty determinations were made on juices from the normal animal. If sufficient pepsin was present, an acidity of 0.10 per cent caused a solution of fibrin in 3.2 hours. Between this acidity and 0.21 per cent the activity periods varied from 2 to 4.5 hours, the average being 3.4 hours.

After parathyroidectomy eight experiments were obtained before the animal died; these may be summarized briefly.

First Experiment

Highest acidity of digest 0.17 per cent, lowest, 0.10 per cent; average activity 5.4 hrs.; number of determinations 6.

Second Experiment

Highest acidity 0.15 per cent; lowest acidity 0.11 per cent; average activity 4.7 hrs.; number of determinations 5.

Third Experiment

Highest acidity 0.15 per cent; lowest acidity 0.10 per cent; average activity 5.8 hrs.; number of determinations 7.

Fourth Experiment

Highest acidity 0.15 per cent; lowest acidity 0.12 per cent, average activity 6.2 hrs.; number of determinations 3.

Fifth Experiment

Highest acidity 0.16 per cent; lowest acidity 0.10 per cent; average activity 6.4 hrs.; number of determinations 7.

Sixth Experiment.

Highest acidity 0.16 per cent; lowest acidity 0.10 per cent; average activity 6.3 hrs.; number of determinations 6.

Seventh Experiment

Highest acidity 0.17 per cent; lowest acidity 0.11 per cent; average activity 6.8 hrs.; number of determinations 4.

Eighth Experiment

Highest acidity 0.14 per ; cent lowest acidity 0.09 per cent; average activity 7.9 hrs.; number of determinations 4.

Addition of acid does not affect materially the activity period, for on the sixth day a juice of 0.10 per cent had an activity of 7 hours, the same juice made up to 0.16 per cent had an activity of 8.5 hours. Again on the seventh day 0.11 per cent drove the reaction in 8.2 hours, and although the acidity was raised to 0.16 per cent, the activity remained 8.5 hours.

Many experiments could be cited to show that the addition of acid to the juice does not increase its efficiency towards the digestion of fibrin. However, this does not mean that the addition of acid might not accelerate the digestion *in vivo*. Since the conditions in the test tube and the stomach are so very different, no time will be wasted in speculating on this point. This topic will be closed by giving one set of experiments made on cat no. 23 two days after parathyroidectomy (page 40).

Such experiments show conclusively that while the reduction in the hydrogen ion concentration may have some effect on the activity, by far the greater factor is the decrease of the pepsin.

Hours after feeding	Free acidity of digest	Hours for complete digestion
1–4	.117	9.0
4–6	.073	5.5
6–9	.038 juice alone .180 juice and acid	6.0 5.7
9–12	.063 juice alone .166 juice and acid	6.2 7.0
12–19	.097 juice alone .175 juice and acid	5.7 5.7
19–27	.063 juice alone .175 juice and acid	7.0 4.7

5. Relation of the Secretion to Symptoms. — Having determined that there are certain well marked changes in the juice following the removal of the parathyroid glands, the next question of interest is the relation of these changes to the symptoms. Do they antedate the symptoms? Do they go hand in hand with them? Perhaps they have no relation at all to them and the whole affair may be sufficiently explained by the moribund condition of the animal?

Before attempting to answer these questions it may not be amiss to summarize the syndrome in cats. The first symptom to appear is a frequent shaking of the front paw or of the animal as a whole. This manifests itself often 3 to 12 hours before any noticeable tremors occur and is a sure index of the initiation of the syndrome. Following may come many different symptoms: tremors with almost constant tetany of a mild grade; intermittent convulsions, in the intervals of which the animal is quite normal; stiffness, accompanied by hyperexcitability and dilation of pupils; or finally the animal may pass quickly into a state of depression without any nervous symptoms. Death results either from asphyxia attendant upon a respiratory spasm or else from general depression. If the animal is watched while in the convulsive state and given artificial respiration, it will usually pass into the stage of depression and die in this manner.

Hence the asphyxial death may be regarded as an accidental one, while the true close of the syndrome is to be found in the depression death. There are then two significant points in the symptom complex, the initiation of the tetany, and the replacement of the tetany by depression. An attempt will be made to show that at these points there is also a change in the secretion. During the stage of active tetany or hyperexcitability, the individual factors are so variable that it is not safe to attempt to trace a relation between the secretion and symptoms.

In six of the cases the advance of symptoms was so slow, that a normal or partially normal secretion was obtained for a while, which then gave way to the parathyroid type. In two of the cases the onset was so rapid as to overwhelm the animal, and death resulted 4 to 6 hours after the first meal was given. In these cases there was almost total suppression of secretion, so nothing is known of the character of the juice. The remaining cases showed marked symptoms before feeding, so that they were of no value in determining the effect of the onset of the disease.

Of the six cases referred to above, only one will be cited and considered in detail. The history of no. 26 shows that on the first day after the removal of the glands the animal ate voluntarily—a circumstance which does not occur after symptoms have set in—and that it developed slight tremors one hour after feeding. The juice secreted during this hour was normal in character, but smaller in quantity. During the succeeding hours the activity and quantity fell, but the acidity maintained itself. The symptoms had increased so that at the end of the tenth hour the animal was suffering from strong tetany. On May 24 convulsions made their appearance, and the greatly depressed condition of the secretory mechanism is obvious at a glance.

Now as to the improvement in secretion with the approach of the depression stage, the evidence is not so complete. This is due to many causes, chief among which is the fact that a smaller number of animals fulfilled these conditions. Many died of asphyxia, resulting from convulsions at times when artificial respiration could not be given; others were so weakened by the tetany, that the depression stage did not last sufficiently long

TABLE II

CAT 26. HOURS AFTER FEEDING

		1	2	3	4	5	6	7	8	9	10	11	12
May 21	Quantity	3.90	3.40	3.00	3.05	1.30	0.90	0.70					
Cat normal	Acidity, free	.420	.449	.449	.468	.312	.312	.058					
	" total	.468	.498	.488	.508	.361	.361	.166					
	Activity	4	4	3	$2\frac{1}{2}$	$2\frac{1}{4}$	$2\frac{1}{4}$						
May 23	Quantity	2.40	2.00	2.20	1.40	1.70	1.75	1.20	0.40	1.20	0.80	0.30	0.80
	Acidity, free	.400	.429	.439	.429	.429	.429			.312	.312	.254	.254
Fourteen hrs. after parathyroidectomy. Ate voluntarily.	" total	.468	.508	.488	.459	.459	.488			.361	.361	.351	.351
	Activity	4	8	$8\frac{1}{2}$	$4\frac{3}{4}$	$4\frac{3}{4}$	$5\frac{1}{4}$		$4\frac{1}{2}$	5	5		
May 24	Quantity	0.70	1.20	1.20	1.10	1.80	1.70	1.30	1.20	0.70	0.60	0.60	
Fed forcibly. Tremors and tetany almost continuous throughout day.	Acidity, free	.254	.254	.410	.410	.420	.420	.400	.400	.351	.351	.351	
	" total	.332	.332	.478	.478	.478	.478	.449	.449	.429	.429	.429	
	Activity	10		$6\frac{1}{2}$		$8\frac{1}{2}$		11		$6\frac{1}{2}$			
May 25	Quantity	2.30	1.88	1.72	1.42	1.15	1.20	1.25	0.95	0.65	0.52	0.41	0.41
Fed forcibly. Animal relaxed but depressed. Sitting up at fifth hour.	Acidity, free	.429	.429	.371	.429	.420	.420	.390	.390	.312	.312	.156	.156
	" total	.488	.488	.429	.508	.468	.468	.468	.468	.371	.371	.234	.234
	Activity	$4\frac{1}{2}$		4		$5\frac{1}{2}$		$3\frac{1}{2}$		9			

for observations. However, evidence on this point is furnished by five animals, nos. 17, 24, 26, 27, and 29.

Inspection of the table of cat no. 26 just given shows that on May 25 the animal was well relaxed and comparatively free from hyperexcitability. The improvement in the juice is so obvious that no comment need be made.

These facts are shown perhaps a little more clearly in the protocol of no. 27. The summary of the runs for May 26, 27, and 30 are given. It will be noted that in spite of the moribund condition of the animal on May 30, the secretion, as to acid, was much better than four days previous. The pepsin and the quantities were practically the same. As compared with May 27, a day on which the animal had convulsion after convulsion, the juice is not only higher in acid, but much greater in quantity.

Cat No. 27, Parathyroidectomized May 22, Secretion of Gastric Juice for four Hours after forcibly feeding Standard Meal of Meat.

Quantity		Free acidity	Total acidity	Activity	Pepsin [1]
May 26	5.9	.068	.151	slight	4.7
May 27 [2]	2.0	.019	.097	0	4.7
May 30 [3]	4.3	.185	.312	4½	5.0

[1] Pepsin determinations were made by adding acid to the juice.
[2] Cat had frequent convulsions throughout the day.
[3] Cat weak, respirations slow, died eighteen hours after feeding, no food in the stomach.

Such evidence, if not conclusive, indicates strongly that with the passing of the nervous disturbances an improvement in secretion occurs.

This part of the paper should not be closed without specific reference to the possibility that all the changes are due to the moribund condition of the animal and have no specific relation to the removal of the glands. If the above contention be allowed, that an improvement in secretion occurs in many cases just before a depression death, this would constitute final refutation of the supposition. However, a table was constructed similar to Table I, in which the quantities, acidities, and activ-

ities of the juices obtained from meals eaten voluntarily by the parathyroidectomized animals were summarized for a period of 6 hours. Fifteen of the cats ate one or more meals voluntarily.

Activity

9 showed depression from $\frac{1}{2}$ to 4 hours.
4 showed no change.
1 showed acceleration.
1 no determinations.

Total Acidity

5 showed depression greater than .05 per cent.
The variations in the remainder were within 0.05 per cent of normal, some above, some below.

Quantity

1 depressed.
3 slightly elevated.
Remainder about normal.

Active Secretion Period

This was lengthened in all cases from 1 to 8 hrs.

These facts point unmistakably to a lowering of the pepsin concentration before the cells become so depressed as to be unable to keep up the quantitative output.

If still further evidence is needed that we have a specific depression of the secretory apparatus, it could be found in an examination of the secretions from the meals just preceding death. Any number of cases could be cited where the animal continued to put out a juice which compared favorably both quantitatively and qualitatively with those of the days previous.

6. Effect of Injecting Calcium Lactate. — Injections of calcium lactate were used in six cases to relieve the symptoms with the idea of protecting the animal, so that further studies might be made. In three of the cases the injections were made into the heart, in the others they were made subcutaneously.

Animals 16 and 19 were suffering with only mild attacks of tetany, and the changes in the secretions were too slight to be considered significant.

Cat Number 17

December 20, Parathyroidectomy
December 22, *Activity*
1–7th hr. of secretion.....5 hrs.
8–9th " " " .....6 hrs.
$9\frac{1}{2}$ hrs. 5 c.c. Lactate into the heart.
December 23, *Quantity*
Same the day previous.
Acidity
Slightly higher.
Activity
1–5th hr. of secretion.....$3\frac{1}{2}$ hrs.
5th hr. on .....5 to 6 hrs.

Cat Number 18

The morning following parathyroidectomy, the animal was prostrated, being completely paralyzed in the hind limbs. Six cubic centimetres of calcium lactate were given into the heart, after which the symptoms gradually improved, so that at the end of the sixth hour the cat was well relaxed and able to walk about the room.

The secretion was as follows:

First hour, quantity 0.2 c.c.
Second hour, quantity 0.58 c.c.; free acid 0.078 per cent; total acid 0.175 per cent; pepsin $2\frac{3}{4}$ hours.
Fifth hour, quantity 1 c.c.; free acid 0.332 per cent; total 0.527 per cent; activity $3\frac{1}{4}$ hrs.

The transition to a true secretion occurred at the beginning of the fifth hour. The juices of the third and fourth hours resembled that of the second in all respects. The inference is that without the calcium no secretion worth mentioning would have been secured.

The improvement in the secretion in the case of cat no. 21 was so striking as to warrant the introduction of a rather complete protocol of the day of the injection and the one following (Table III). Examination of the table will show a striking rise in the rate of secretion following the injection, even though it was made at the end of a secretion period. It is further noticed

that the improvement is not confined to the quantity of juice, for there is an increase in the acidity and activity also. In the two last respects the juice is normal.

TABLE III

CAT NO. 21. PARATHYROIDECTOMY, JANUARY 8

January 10						January 11				
Hours of secretion	Quantity	Acidity		Act.	Remarks	Quantity	Acidity		Act.	Remarks
		Free	Total				Free	Total		
1	0.30	.263	.302		Marked tremors.	0.50	0.468	.527	2	Well relaxed
2	0.25	.263	.302	4	Feet stiff.	1.90	0.468	.527		
3	1.15	.263	.302		Unable to stand.	1.90	0.468	.527		
4	0.63	.420	.478	$4\frac{1}{4}$		1.65	0.459	.547	$2\frac{1}{4}$	
5	0.62	.420	.478			1.40	0.488	.566	$4\frac{1}{4}$	
6	1.15	.390	.508			1.10	0.468	.586		
7	0.45	.390	.508			1.10	0.449	.527		
8	0.45	.390	.508	3 to $3\frac{1}{4}$		1.20	0.449	.527		
9	0.40	.390	.508			0.86	0.420	.468		
10	0.40	.390	.508		Animal prostrated	0.86	0.420	.468		
11 [1]	1.60	.449	.547	$4\frac{3}{4}$		0.86	0.420	.468		
12	1.60	.449	.547			0.35	0.263	.332		
13	0.90	.361	.439			0.26	0.263	.332		
14	0.40	.361	.439							
15	0.31	.117	.234		Animal sitting up.					
16										

[1] Six cubic centimetres of five per cent calcium lactate injected.

Of course the data at hand are not so complete as one might wish, but they certainly suggest that in the advanced stages of tetany calcium administration improves the secretion of gastric juice.

7. Site of the Depression. — As to the site at which the secretory mechanism is depressed no direct data are offered. In fact, this problem is now being investigated. Our knowledge as to the normal quantitative value of the nervous and chemical phases of gastric secretion is not so complete as one might wish. Further, it is even contended by some that the gastric hormone (gastrin) may act by way of intrinsic nerves rather than on the cells direct. If we assume with Pawlow that the extrinsic nervous mechanism is mainly responsible for the first hour's secretion and that the remainder arises in response to chemical excitants (the gastrin of Edkins[1]), we may look to four sources for the depression.

(*a*) The gastric cells may be so poisoned with "circulating toxins" as to be unable to respond to any stimulus.

(*b*) There may be some interference with the formation and the action of the hormone, or else an actual destruction of it in the blood stream may occur.

(*c*) Blocking of the reflex arc at any point in its course or the development of inhibitory impulses from some central source would offer sufficient explanation for the depression.

(*d*) Circulatory disturbances.

The evidence available points towards some disturbance of the nervous phase of the secretory mechanism. In many of the cases the acid output reached the same height as that from the normal cells. However, this height would be attained only after the fourth or fifth hour instead of after the first. This suggests that they are not receiving sufficient stimuli rather than that they are suffering from an intoxication. We would not expect an intoxicated cell to reach the efficiency of a normal one.

The improvement of the secretion on the disappearance of the nervous symptoms is certainly more readily explained by considering that the impairment is associated with these disturbances than on other hypotheses. If we are dealing with a circulating toxin which acts by depressing the cells or incapacitating the hormone it is hard to see why there should be a smaller quantity of this present just preceding death. On the other hand, many explanations might be advanced for the pass-

[1] Edkins: Journal of physiology, xxxiv, p. 133.

ing of the tetany symptoms. Logically, then, this seems to be the more plausible and fruitful view to adopt as a working basis. To analyze the situation further is unwarranted, since there are no experimental facts for guidance.

IV. Summary

(1) The performance on the thyroid-parathyroid apparatus of an operation which consists of its isolation and the separation of its blood supply, leaves the gastric secretory mechanism slightly more irritable on the following day. This irritability is shown by maintenance of the quantitative output, an increase in the activity of the juice, and by the fact that the period of active secretion is slightly lengthened. The persistence of the secretion is attributed to local reflex stimulation by small particles of residual food, which are unable to cause secretion normally.

(2) After parathyroidectomy the following conditions exist:

(*a*) The quantity of gastric juice is lessened, and in some cases it may be entirely suppressed.

(*b*) There is depression of the free and total acid and this is attributed to a smaller hydrogen ion output by the cells rather than to secondary neutralization by the mucus, though the evidence on this point is not final.

(*c*) The digestive power (activity of the juice when diluted with water) is markedly lowered. This may be partially due to lack of available hydrogen ions, but it seems to depend chiefly on a specific decrease of the pepsin.

(*d*) The period of active secretion is greatly lengthened.

(3) There is a shifting from the normal to the parathyroid type of secretion on the development of tetany symptoms. During active tetany no relation between the secretion and the symptoms has been traced.

(4) The evidence seems sufficient that on the replacement of the tetany symptoms by depression there is an improvement in the secretion of the juice. Hence the moribund condition of the animal can not be advanced as sufficient explanation for the alterations in the juice in tetany.

(5) Injections of calcium salts improve the secretory mechanism. This is shown best in the advanced cases.

(6) The possibility of the depressing influence attacking the secretory mechanism through its nervous connection is considered.

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FIBRINOGEN

I. An Investigation Concerning Its Origin and Destruction in the Body

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IN this communication will be found observations upon the fibrinogen of the blood in man and the dog, in health and disease. Certain experiments are cited which bear upon the question of the origin of blood fibrinogen and the factors which act so rapidly and effectively to maintain the fibrinogen level above the margin of safety.

It is not necessary to discuss the views of the recent workers concerning the origin of fibrinogen, as this has been done very concisely in a recent paper by Meek.[1] In a word, three theories have been championed by various investigators: (1) that fibrinogen is formed by the bone marrow and is perhaps dependent upon the white cells; (2) that fibrinogen is formed by the intestine; (3) that fibrinogen is produced by the liver.

It has long been known that liver injury (chloroform, phosphorus, etc.) is associated with a great drop in fibrinogen. Moreover, it has been shown by Whipple and Hurwitz[2] that the drop in fibrinogen is proportional to the amount of liver injury and that liver repair is followed by a rapid return of the fibrinogen to normal or even above normal. These observations make one feel that the liver is a most important organ in maintaining the fibrinogen balance. It may be objected, however, that this acute liver injury with the attending coagulative necrosis and tissue destruction may be associated with a great demand upon the

[1] Meek: This journal, 1912, xxx, p. 161.

[2] Whipple and Hurwitz: Journal of experimental medicine, 1911, xiii, p. 136.

fibrinogen supply and perhaps an escape of a ferment capable of destroying fibrinogen. These points will be touched upon later.

It will be recalled that the fibrinogen curve does not drop sharply following chloroform injury, but may require two or three days to reach its lowest level (Table VI). From recent work on the ferment lipase (Whipple [1]) and the liver excretion of phenoltetrachlorphthalein (Whipple, Peightal, and Clark [2]) it is clear that the liver injury following the anaesthesia is immediate. It may be argued that the supply of fibronogen is only slowly depleted and lasts for a time after the liver is thrown out of function. Against this explanation stands a large series of experiments by many workers (Doyon with his co-workers and Nolf [3]), which indicate that liver extirpation is followed by complete or almost total disappearance of the fibrinogen within a short period (1 to 2 hrs.). These observations on liver removal are contradicted by the experiments of Lilienfeld,[4] Meek,[5] and the writer.

In the early part of this work it was thought possible that some injurious agent might heap up in the blood stream during the second to fourth day after the chloroform poisoning, which in itself could further injure the liver or destroy fibrinogen. With this point in view several experiments were performed as follows. A large dog (20 to 40 lbs.) was severely poisoned by chloroform anaesthesia for two to three hours and on the second or third day following was bled to death from the carotid. This blood (1000 to 1500 c.c.) was defibrinated and after filtering through cotton was injected intravenously into a small puppy (weight 1 to 2 lbs.). The pups were bled from the carotid at short intervals to permit at intervals a complete replacement of the pup's blood by the defibrinated chloroform blood. This procedure occupied one-half to one hour in each case and there was absolutely no evidence of any liver injury (autopsy on second day after transfusion) nor of destruction of fibrinogen. The fact which impressed us was the tre-

[1] Whipple: Johns Hopkins Hospital bulletin, 1913, xxiv, p. 357.

[2] Whipple, Peightal, and Clark: Johns Hopkins Hospital bulletin, 1913, xxiv, p. 343.

[3] Nolf: Archives internationales de physiologie, 1905, iii, p. 1. Doyon: Journal de physiologie et de pathologie générale, 1912, xiv, p. 229. Doyon and Kareff: Comptes rendus de la Société de biologie, 1904, lvi, p. 612.

[4] Lilienfeld: Archiv für Physiologie, 1892, p. 550.

[5] Meek: *loc. cit.*

mendous capacity of the normal pup to reproduce fibrinogen after the blood vessels were washed quite free. This is brought out clearly in the following paper (Goodpasture).

Method

The various methods of fibrinogen or fibrin determination are subject to many errors. The method of whipping the whole blood will give results which are too high because of included cells. Salt precipitation is very inaccurate and incomplete. The ideal method would be the clotting of clear oxalate plasma by means of equal volumes of fresh serum. This causes dilution of the clot, which is not too tough to be teased, washed, and dried. We have used this method to check the heat coagulation method, and several of these observations given in the tables II and V below indicate a close harmony in results. The heat coagulation method is quite accurate in plasmas where the fibrinogen is not extremely low. Under such conditions (phosphorus and chloroform) the method may give too low readings and should be controlled by the plasma-serum coagulum.

In our earlier observations B–1 to B–46 and published experiments (Whipple and Hurwitz [1]) the method consisted in plasma coagulation by heat at 58° to 60° C. after neutralization to litmus using 5 per cent acetic acid. The precipitated fibrinogen was centrifugalized, washed with hot and cold water, alcohol and ether, finally thrown upon a weighed filter, and dried at 110° C. The neutralization of the plasma introduced a personal factor and possibilities of considerable error.

The method used in the greater number of the observations tabulated below may be outlined as follows. Clear plasma was measured into a centrifuge tube and placed in a water-bath at 58° to 60° C. for 20 minutes. The precipitate was collected by centrifugalization, washed thoroughly by cold and hot water, alcohol and ether; then washed into a Gooch crucible and dried at 110° to 115° C. to constant weight. This method is fairly rapid and simple and gives constant results in our hands, often

[1] Whipple and Hurwitz: *loc. cit.*

controlled by the plasma-serum coagulum method, which is not always available from lack of fresh serum.

The blood was drawn directly into oxalate by canula in a vessel (dog) or by aspirator needle in vein (man) or heart shortly after death. The method of Jeger [1] was used for the Eck fistula. This consists in joining the portal and vena cava as in a lateral entero-enterostomy, using a special type of clamp. The portal vein is then ligated at the hilum of the liver. The hepatic artery was ligated at the hilum in a manner previously described (Whipple and Sperry [2] to exclude collaterals.

The "head circulation" experiments were done under ether anaesthesia using the Meltzer-Auer insufflation method. A screw clamp was placed on the aorta just beyond the origin of the subclavian artery. The mammaries, the collaterals in the recti and along the costal margin were secured by deep sutures and clamps.

In all cases where not noted the vena cava was ligated above the diaphragm. When properly done in a strong animal this will establish a very vigorous circulation in the head, forelegs, and thorax. Anaesthesia is discontinued and $\frac{1}{8}$ morphia given intravenously. Under favorable conditions the heart will beat very vigorously for three to five hours, so that the tongue and mucous membranes will be a bright crimson color. When the circulation fails it comes on very suddenly with sometimes muscular tremor and twitchings as a premonitory symptom. At the end of an experiment the blood was drawn immediately from the auricle.

The dry weight per cent was determined by collecting two specimens of blood at the time of fibrinogen determination. The blood (about 1 c.c. in amount) was collected in weighing bottles, weighed at once, dehydrated by dry heat at 110° to 115° C. to a constant weight, and the percentage calculated. Two specimens were always taken at each observation and rarely varied more than .1 per cent.

The tabulated results (Table I) show the effect of starvation which does not influence the blood fibrinogen. All these dogs were in good health at the time that the blood was obtained, as a rule following a fast of 12 to 14 hours to insure a clear plasma.

[1] Jeger: Centralblatt für Chirurgie, 1912, xxxix, p. 465.

[2] Whipple and Sperry: Johns Hopkins Hospital bulletin, 1909, xx, p. 278.

During the periods of starvation the dog was kept in close confinement and allowed to drink water freely. After this period of 8 to 16 days the dog was put on a full diet and on the third day following showed a slight decrease in blood fibrinogen. On the

TABLE I

NORMAL DOGS — FIBRINOGEN

No.	Acetic acid 5% in drops	Plasma taken	Fibrinogen gm. per 100 c.c.	Remarks
B–1	11	25 c.c.	.4928	
"	9	20 c.c.	.2090	1 month later
B–5	9	25 c.c.	.8672	
"	—	25 c.c.	.6900	8 days later
"	8	25 c.c.	.5936	5 weeks later
B–6	9	25 c.c.	.2612	
"	—	25 c.c.	.6088	10 days later
"	8	25 c.c.	.5332	Starvation 8 days previous
"	8	25 c.c.	.4560	Full diet 3 days since fast
"	20	25 c.c.	.5404	Starved 2 days. 11 A.M., bled
"	19	25 c.c.	.5712	Food at 1 P.M. Bled 4 P.M.
B–21	8	25 c.c.	.7552	Starvation 16 days previously
"	10	25 c.c.	.5576	Full diet 3 days since fast
B–16	—	25 c.c.	.4708	
"	13	25 c.c.	.2516	3 weeks later
B–41	17	25 c.c.	.2488	
B–31	—	25 c.c.	.5864	
B–46	16	25 c.c.	.3200	

other hand, after a short fast and fibrinogen determination the dog was fed at 1 P.M. and a second determination at 4 P.M. showed a slight rise in fibrinogen content.

The individual variations in perfect health are astonishing and we can ascribe no reason for this. It would be very interesting to

follow a dog from day to day and chart the fluctuations in fibrinogen, but the amount of blood required is considerable and this by itself would introduce a disturbing factor — it would no longer be a normal fibrinogen curve but one of secondary anemia and repair.

Table II gives further observations on fibrinogen in strong, healthy dogs. These dogs show wide fluctuation of blood fibrino-

TABLE II

NORMAL DOGS — FIBRINOGEN

No.	Plasma	Fibrinogen gm. per 100 c.c.	
C–13	25 c.c.	.3568	No acetic added [3]
"	25 c.c.	.3600	Acetic to faint acidity [3]
"	25 c.c.	.1984	1 month later; heat coagulation [1]
"	10 c.c.	.2260	Fibrin diluted and clotted by serum [1]
"	25 c.c.	.5376	4 months later
"	25 c.c.	.3872	6 months later
C–15	25 c.c.	.4224	5 drops acetic used [2]
"	25 c.c.	.3968	6 drops acetic used [2]
"	25 c.c.	.2644	6 weeks later
C–26	25 c.c.	.6604	Heat coagulation [1]
"	5 c.c.	.7720	Diluted and clotted by serum [1]
C–39	25 c.c.	.3844	

[1] Parallel observations with same plasma to contrast the heat method with plasma-serum coagulation.
[2] Observations on same plasma; different workers.
[3] Same plasma and worker.

gen from week to week. Some of the checks and controls of the heat method are given, and it will be found that the error does not exceed 25 mg. Even with careful plasma clotting by serum and washing of the clot, it is probable that the final reading is too high, as the clot probably includes some proteid besides the fibrin. The correct reading surely lies close to this and between

it and the heat coagulum result, which is admittedly too low. Two specimens of plasma done by the heat coagulation method by the same worker will rarely vary as much as 10 mg., but done by separate workers of little experience may vary as much as 25 mg. (see Table II). The observations, too, show that small amounts of acetic acid do not introduce any factor of error, but acid to a distinct red litmus reaction will cause considerable increase in heat coagulation.

The two tables, I and II, give thirty observations on normal animals. The average is .4663 gm. per 100 c.c. plasma or .466 per cent. The fluctuations are great and run from a minimum of .1984 gm. to a maximum of .8670 gm. The limits of normal may be placed between .20 and .80 per cent. Individual fluctuation is great even in a short space of time, .2612 to .6088 gm. within 10 days. We have no explanation for this remarkable variation, but feel that the method is not at fault. This variation must be taken into consideration in all work concerning the fibrinogen variation in dogs.

Table III shows that dogs suffering from various diseases (pancreatitis, icterus, distemper) have normal amounts of fibrinogen. Perhaps in the acute intoxications there may be a slight rise, but the wide fluctuation of fibrinogen in health must be kept in mind in drawing deductions. The dogs with Eck fistulae show a normal fibrinogen.

These observations on fibrinogen in human blood are included because the recorded data upon this point are rather scant (Tables IV and V). It is of interest to note that the human cases do not have wide fluctuations as is the case in dogs. We may perhaps place the normal limits as .300 and .600 gm. with the usual finding of .40 to .50 per cent. It may be argued that cases of eclampsia are suffering from acute intoxication, which usually reacts upon the liver and perhaps upon the fibrinogen. It might cause irritation and overproduction with an excess of fibrinogen, but this does not seem to be the case.

In a recent paper (Whipple, Mason, and Peightal[1]) we have emphasized the importance of a low fibrinogen in cases of hepatic

[1] Whipple, Mason, and Peightal: Johns Hopkins Hospital bulletin, 1913, xxiv, p. 207.

disease. In cases of hepatic disease a low fibrinogen indicates a grave condition and speaks for a decided hepatic insufficiency. Fibrinogen may be normal even in some fatal cases of cirrhosis (Table IV). It is not influenced by extreme icterus of long standing nor by great invasion of secondary cancer nodules with considerable destruction of liver parenchyma.

As is well known, the fibrinogen content may reach its maximum in lobar pneumonia (Table V), and the tough clots so characteristic of this disease are, of course, dependent upon this fact.

TABLE III

FIBRINOGEN IN ABNORMAL CONDITION (DOGS)

No.	Acetic acid 5% in drops	Plasma	Fibrinogen per 100 c.c.	Remarks
B–1	9	20 c.c.	.2090	Normal
"	15	25 c.c.	.5320	Blood drawn on second day of acute hemorrhagic pancreatitis. Recovery 1 week
B–3	7	25 c.c.	.3364	Chronic pancreatitis
"		25 c.c.	.3008	Obstructive jaundice 8 days
B–5	8	25 c.c.	.5936	Normal
"	15	25 c.c.	.5248	Acute pancreatitis, 2 days duration, recovery
B–13	13	25 c.c.	.6768	Distemper fatal
B–36	12	25 c.c.	.5456	Eck fistula 2 weeks
C–21	4	25 c.c.	.2720	Eck fistula 3 weeks
"	0	25 c.c.	.2616	10 days later

Great amounts of fibrin are formed, dissolved, and deposited constantly in the lung during lobar pneumonia, and it is possible that this demand for large amounts of fibrinogen calls the organs forming it into great activity with consequent overproduction. It is possible, too, that the intoxication associated with the disease may stimulate an overproduction of fibrinogen. The liver shows evidence of injury in pneumonia-parenchymatous degeneration with occasional liver necrosis. This slight grade of injury may actually stimulate the parenchyma cells to overactivity, or we may

TABLE IV

HUMAN CASES

Normal or approximately so

Name	Fibrinogen	Plasma	Diagnosis
Aro	.400	20 c.c.	Senility
Massey	.4280	20 c.c.	Slight chronic nephritis
3667	.3850	25 c.c.	Vomiting of pregnancy
3672	.6176	25 c.c.	Eclampsia
M.	.5912	25 c.c.	"
Slachter	.5272	25 c.c.	Large liver
Schwab	.5750	20 c.c.	Large liver — bleeding
			HEPATIC DISEASE
3726	.0336	25 c.c.	Chloroform poisoning — liver necrosis
B. V.	.1170	20 c.c.	Cirrhosis: symptoms. Phenoltetrachlorphthalein very low
3616	.0424	25 c.c.	Cirrhosis — fatal bleeding
3657	.3576	25 c.c.	Cirrhosis — portal obstruction
Reifschneider	.3408	25 c.c.	Cirrhosis — no symptoms
Neizer	.3440	10 c.c.	" " "
Woods	.4080	10 c.c.	Icterus 3 months — gall stones
Jones	.4700	20 c.c.	" tumor of pancreas
White	.2480	20 c.c.	" 4 months cancer
Fisher	.5160	10 c.c.	Liver, cancer metastasis (April 5)
"	.4060	20 c.c.	Liver necrosis metastasis (April 9)
Carroll	.7200	25 c.c.	Liver metastasis, icterus, cirrhosis (July 13)
"	.7320	10 c.c.	" " " " (July 18)
"	.5192	25 c.c.	" central necrosis (July 20)

say that this poison acts as an irritant in a suitable dilution when in sufficient concentration it may cause necrosis or degeneration. There is some experimental evidence that very small doses of hepatic poison may stimulate the liver to overfunctional activity and that fibrinogen may rise above normal at such times.

TABLE V

HUMAN CASES, CACHEXIA

No.	Fibrinogen	Plasma	Diagnosis
3686	.1776	25 c.c.	General sarcomatosis — liver normal
3673	.1056	25 c.c.	Miliary tuberculosis
3751	.0823	25 c.c.	Miliary tuberculosis — June 28
3751	.1104	25 c.c.	Autopsy July 12
3665	.2184	25 c.c.	Chronic nephritis
		PNEUMONIA	
3705	.9016	25 c.c.	Lobar-mixed hepatization
Newton	.9110	20 c.c.	Lobar-mixed hepatization, fatal seventh day
3671	.5120	25 c.c.	Acute hemorrhagic colitis
		ANEMIAS	
3916	.1420	20 c.c.	Pernicious anemia
3724	.4032	25 c.c.	Aplastic anemia — heat method
3724	.4080	25 c.c.	Fibrin method — serum coagulation
Marchant	.2850	20 c.c.	Aplastic anemia. Hb. 13%. R. B. C. 800,000. W. B. C. 1,200

The low fibrinogen in cases of cachexia (Table V) is not easy to explain. The liver is not at fault as far as the microscope can show, although it may contain miliary tubercles or tumor nodules. There are so many factors which may enter into this equation that it is useless to speculate upon it.

The group of anemias is of considerable interest and the findings here appear to disprove beyond any reasonable doubt the bone marrow theory of fibrinogen production. Two cases of typical aplastic anemia with a rapidly fatal course (one with autopsy and aplastic marrow) show a fibrinogen which is normal and low normal. The patients died from lack of blood cell production

TABLE VI

FIBRINOGEN CURVES IN CHLOROFORM POISONING

Normal C–19			Eck Fistula C–21	
Jan. 30	Fibrinogen	Dry weight	Fibrinogen	Dry weight
1.45 P.M.	.6604	17.2% 17.3%	.2616	18.7% 18.7%
CHLOROFORM ANAESTHESIS $2\frac{3}{4}$ HR. (11 A.M. TO 1.45 P.M.)				
7 P.M.	.6084	16.8% 16.8	.1768	18.3% 18.2
Jan. 31 10 A.M.	.4044	16.8% 16.7	.1756	18.2% 18.3
Feb. 1 3 P.M.	.1924	15.1% 15.0	.0176	19.3% 19.3
Feb. 3	.0928	14.2% 14.2	.3784	16.6% 16.6
Feb. 20	Recovery complete		.2672	Death, convulsions

and it seems hard to imagine a normal fibrinogen under these conditions if the elaboration of fibrinogen was in any way dependent upon the bone marrow.

Table VI shows the drop in the fibrinogen curve after a long chloroform anaesthesia ($2\frac{3}{4}$ hr.) in a normal dog and one with an Eck fistula. Blood was drawn at the end of the anaesthesia and again five hours later. The dry weight of the whole blood was

taken at the same time to control loss or gain in blood concentration. It will be seen that the drop was more prompt in the Eck fistula dog than in the normal; the same was true of recovery and repair. It will be pretty safe to assume a more marked injury to liver parenchyma in the normal dog.

Why is it that with an Eck fistula and hepatic artery ligation, which excludes the liver, there is little or no drop in blood fibrinogen (Table VIII), whereas following an acute liver injury (chloroform) there develops in the same period a definite fibrinogen drop? This suggests that at least a part of the drop is to be

TABLE VII

Incubation of Plasma at 38° C. Fibrinogen in Grams per 100 c.c.

	Control	Incubation 15 hr.
Normal Dog C–13	.5376	.4960
Chloroform Dog C–59	.0170	.0132
Mixture of plasma, equal parts C–59 + C–13	.2565 (estimated)	.2465

accounted for by the actual liver injury and cell necrosis—a type of coagulative necrosis. We may account for this using up of fibrinogen in two ways. (1) Actual use of the fibrinogen in the change which develops in the cell protoplasm as it undergoes hyaline necrosis. (2) Escape of a ferment from the injured liver cells (as is the case with lipase) which is able to dissolve or digest fibrinogen. If this is a real difference and not due to any error in experiment or method, we are driven to the conclusion that the actual cell injury does in some obscure manner deplete the blood of its fibrinogen, for the following type experiment shows that there is no active fibrinogen destroying ferment (Table VII).

Plasma from a normal dog and one severely poisoned with chloroform were taken and the fibrinogen estimated as usual (control). A measured amount of each plasma and a mixture of equal parts were placed in the incubator (38° C.) for 15 hours. At the

end of this time the fibrinogen in all three specimens was determined as usual. There is a small loss of fibrinogen in all specimens, slightly more in the normal fraction, but this can have no significance. When an active fibrinolytic ferment is present in experiments or disease it acts with great rapidity on its own or foreign fibrin and very slowly if at all on the fibrinogen.

TABLE VIII

Eck Fistula + Hepatic Artery Ligation

No.	Fibrinogen		Dry weight, per cent		Duration of circulation
	Before	After	Before	After	
C–80	.3224	.2552	20.1 20.0	17.9 18.2	3 hr. 50 min.
C–95	.6728	.7400	20.1 20.0	20.4 20.3	5 hr. 20 min.
C–98 [1]	.6544	.7272	20.7 20.7	20.7 20.8	5 hr.
C–105	.3208	.2480	20.2 20.3	18.2 18.3	5 hr. 30 min.

[1] Spleen extirpation during operation.

Tables VIII and IX summarize the experiments with "liver removal." Given a successful Eck fistula, ligation of portal vein at the hilum, also the hepatic artery with its collaterals, it may be assumed that the liver is completely shut off from the other organs. Injection experiments show that there are small collaterals by which injection material or blood can gain entrance to the liver (dog B–48), but at most this is a very slow seepage, which does not suffice to keep the liver alive; often the parenchyma shows evidence of beginning autolysis at the end of the experiment. Functional tests with phenoltetrachlorphthalein show that this drug may appear in *traces* in the bile in such experiments, but in amounts too small to be estimated. Moreover, the dogs all die after a period of four to six hours with characteristic symptoms of intoxication—muscular tremors, twitchings, and

final convulsions. The circulation is excellent up to the very end when the heart stops in diastole.

Under these circumstances there is very little change in the fibrinogen content. Some experiments show a slight fall in fibrinogen, but it will be noted that in these cases there is a lowering of the blood dry weight per cent. Other experiments, in which the blood concentration remains uniform, may show a slight rise in fibrinogen. The blood clotted normally at the end of all these experiments and there was no evidence of fibrinolysis. Granting the liver to be very actively concerned in the maintenance of the blood fibrinogen, we may assume one of three possibilities to account for this. (1) The fibrinogen is not used

TABLE IX

Eck Fistula + Hepatic Artery Ligation

No.	Fibrinogen		Duration of circulation	Remarks
	Before	After		
B–36	.5456	.5856	6 hr. 15 min.	Eck fistula Nov. 20 — hepatic artery ligated Dec. 7
B–48	.1868	.2144	4 hr. 50 min.	Defibrination at beginning (note history below)

up rapidly in the circulation. (2) The fibrinogen may be held in reserve in some other tissue. (3) Some other organ may be able to produce fibrinogen in an emergency. The experiments given below (Table X), in which a circulation through the head, forelegs, and thorax for two or more hours shows a definite fall in fibrinogen, speak for a pretty rapid use or destruction of the circulating fibrinogen. We are led to believe, then, that some other organ or tissue besides the liver may either store fibrinogen for use or be able to produce it in an emergency. When we consider that the "head-thorax circulation" experiments show a drop in fibrinogen and the "liver removal" experiments do not show a pronounced drop in fibrinogen, we are tempted to assume that some of the abdominal viscera are concerned in the puzzle. The

experiments in the following paper (Goodpasture) give evidence that the intestinal tract is concerned.

"Liver Removal" — Defibrination

Dog B–48. Jan. 18. Ether anaesthesia. Operation and production of *Eck fistula.*

Feb. 4. Dog in excellent condition. 11 A.M. Operation with aseptic precautions — ether anaesthesia. The hepatic artery and its branches are ligated securely at the hilum of the liver. 12 M. Operation complete and abdomen closed as usual. 12.15 to 1.50 P.M. *Defibrination* of animal in the usual manner, about 250 to 300 c.c. of blood being removed in each instance. The blood was shaken in a sterile jar with beads until coagulation was complete, filtered through gauze, and finally reinjected intravenously. This was repeated six times. After the last defibrination and reinjection of blood serum 60 c.c. of blood were drawn for determination of *fibrinogen* (0.1868 gram per 100 c.c.).

2.15 P.M. Dog in fine condition with regular pulse. Ether anaesthesia was discontinued at 1.30, but a quarter of grain of morphia given. 3 P.M. Pulse is regular but rather rapid, about 220 per minute. 4.15 P.M. Inspiration prolonged and deep. Mucous membranes and tongue of good color. 4.40 P.M. Death with deep forcible respiratory efforts.

Autopsy performed at once. Blood removed immediately from right ventricle and received into oxalate (see Table IX). *Fibrinogen* determination (0.2144 gram per 100 c.c.). The blood placed in containers without oxalate clotted firmly in a very few seconds, and it was evident that the coagulation time was much shorter than normal. Within 10 minutes a rapid and complete shrinkage of the clot took place.

Within 15 minutes the aorta above the diaphragm was injected with a warm gelatin mass under 100 mm. of mercury pressure. The mesenteric vessels filled at once and the fluid appeared in the right auricle in a few seconds. The injection mass oozed from the cut surface of the liver. Body placed in ice box over night and dissected after complete hardening. Careful dissection showed the Eck fistula to be perfect. The hepatic artery in the hilum of the liver contained a little injection mass due to a tiny collateral running in the gastro-hepatic omentum communicating with the duodenal branches. The adhesions about the surface of the liver

caused by the first operation were filled with injected blood vessels and probably furnished a small amount of blood to the liver. Microscopical section of the liver showed a little central fatty degeneration and atrophy, as is usual in Eck fistula dogs.

In this experiment (B–48) the dog was partially defibrinated after making an Eck fistula and ligating the hepatic artery. Defibrination under normal conditions gives the greatest stimulus to the formation of new fibrinogen, which follows with striking rapidity. The stimulus of defibrination caused little disturbance in this experiment and we find not a fall but a rise in fibrinogen (27 mg. in about 3 hr.) before death. We may assume (Table X) that some fibrinogen was used up during this time, so that it had been formed or stored in some organ other than the liver.

The immediate coagulation of the heart's blood on removal after death speaks for a using up of the normal antithrombin of the blood during the process of defibrination — probably by the action of the introduced thrombin.

This experiment (B–48) makes one other point very clear: that the mechanism which protects the body against any excess of thrombin injected into or formed within the circulation does not necessarily include the liver. The tissues, aside from the liver, can neutralize or destroy large amounts of thrombin, otherwise there would have been intravascular clotting during defibrination. It is known that the introduction of thrombin into the normal circulation may produce an antithrombin wave (Howell[1]), and one is tempted to look at this as a protective mechanism and as the means by which the body can protect itself against thrombin escape into the circulation (thrombosis, etc.). There is good evidence that the liver is very active in antithrombin production. But it is clear that the body has other ways of protecting itself against intravascular clotting when thrombin is present in the circulation.

Splenic Eck Fistula and Hepatic Artery Ligation

Dogs C–31, 32, 33, and 37. Similar operation and findings in each case. Hepatic artery ligated. Eck fistula produced *below* the splenic branch with ligation between it and the fistula. This allowed the

[1] Howell. Personal communication.

splenic and duodenal venous blood to pass through the liver. It was insufficient for life. Dogs did well for six or eight hours and died always within 18 hours. There was no marked drop in fibrinogen during this period (C–37).

C–37	Fibrinogen	Dry weight
Before	.4324	24.8 and 24.8%
After 10 hr.	.3866	27.3 and 27.2%

The blood clotted normally, and firm clots were present in heart and vessels at death. Autopsy showed advanced degeneration and autolysis of liver.

In this group of experiments the liver is cut off from the circulation except for the venous blood, which can flow through the splenic and duodenal branches of the portal vein. This is not sufficient to maintain the liver in functional activity and the organ shows signs of autolysis at autopsy. It was thought that some interesting points might develop under such circumstances, but nothing abnormal in fibrinogen content or blood coagulation

TABLE X

"Head-Thorax Circulation"

No.	Fibrinogen		Dry weight per cent		Duration of circulation
	Before	After	Before	After	
C–97	.3600	.2144	23.4 23.3	20.4 20.4	4 hr. 40 min.[1]
C–100	.2400	.1544	19.1 19.1	18.8 18.9	2 hr. 50 min.
C–13	.3872	.2320	21.8 21.7	17.7 17.7	2 hr. 35 min.
B–16	.2516	.1848	—	—	4 hr. 40 min.

[1]Vena cava inferior not ligated.

could be demonstrated. After a period of 10 hours there is little change in the blood fibrinogen.

Table X gives the results of the "head-thorax circulation" experiments. The aorta clamped below the subclavian, mammaries ligated, and collaterals in recti and along costal margin secured. Vena cava above diaphragm ligated — this gives an active circulation in head, thorax, and forelegs. There is a definite fall in blood fibrinogen during a period of three to five hours, which speaks for a rapid use of fibrinogen. It is possible that these tissues, cut off from the abdominal viscera, are forced to use proteid material which is not commonly called upon except in an emergency. The blood clotted normally at the end of each experiment.

Discussion and Summary

The blood fibrinogen varies greatly in amount in normal dog's plasma. The average falls between .5 and .4 per cent, but in health the extremes may be .2 for minimum and about .85 for maximum. Individual variation from .26 to .60 per cent was noted in a space of ten days. Starvation or feeding does not seem to influence the fibrinogen content. No explanation is offered for this fluctuation in the fibrinogen curve, but it must be taken into consideration when interpreting results.

The blood fibrinogen in man varies much less than in the dog. The normal limits may be placed as .3 and .6 per cent, while the average will fall very close to .500 gm. per 100 c.c. plasma. Fibrinogen is much above normal in pneumonia and septicaemia, reaching .9 per cent. In acute liver injury the fibrinogen falls to a very low level or even zero in some fatal cases. In chronic liver disease the fibrinogen often falls to a very low level and may cause bleeding (cirrhosis). This as well as other evidence makes it reasonably certain that the liver is very active in the formation of fibrinogen and is the most important factor in maintaining a constant fibrinogen balance.

In general cachexia (sarcomatosis, nephritis, miliary tuberculosis) the fibrinogen may be quite low (.1 per cent). The liver may appear quite normal in such cases. A grave cachexia may be associated with cancer of the liver and a normal fibri-

nogen content; so, too, the intoxication associated with uraemia or general carcinomatosis may be associated with normal blood fibrinogen.

Certain aplastic anemias may show a normal fibrinogen content with complete aplasia of the bone marrow. Experiments with chloroform poisoning may be associated with a marked leucocytosis and a very low fibrinogen. These facts seem to show clearly that the bone marrow has no concern with the formation of fibrinogen.

A. Acute chloroform poisoning causes a rapid drop in the fibrinogen curve and the loss at the end of five hours is easily recognized.

B. An Eck fistula plus hepatic artery ligation ("liver removal") in a space of five hours will give no appreciable drop in the fibrinogen curves.

C. Ligation of aorta, vena cava, etc. ("head-thorax circulation"), in an experiment of four to five hours duration will show a decided drop in the fibrinogen content.

The following hypotheses are proposed to explain these three main points:

The fibrinogen in the "head-thorax circulation" is used up pretty rapidly because the entire source of supply is cut off and the tissues may be forced to use this proteid, even if it is not normally consumed in any considerable degree.

In the "liver removal" experiments the circulation is deprived of any participation on the part of the liver, yet the fibrinogen does not fall appreciably. This may indicate a reserve of fibrinogen or the production of fibrinogen by some other organ (e.g., intestines) as there is no reason to suppose any sparing of fibrinogen more than in the "head-thorax circulation."

In the liver poisoning (chloroform) experiments we cannot attain more than *complete* liver paralysis or destruction and scarcely that, as the animals rarely die inside of 24 hours. There is no ferment freed from the injured liver which can destroy the fibrinogen. It is probable that the killed liver cells (coagulative hyaline necrosis) in some way effect a drain on the blood fibrinogen and cause the rapid fall in the fibrinogen curve.

The "liver removal" experiment when combined with defibrina-

tion shows that the body, excluding antithrombin and the liver, has powerful means at hand to neutralize large amounts of thrombin introduced into the circulation.

In conclusion it is a pleasure to express most sincere appreciation to several workers in the laboratory who assisted in many of the experiments — Dr. F. L. Gates, O. E. Utzinger, L. S. Krake, and C. W. Hooper.

FIBRINOGEN

II. The Association of Liver and Intestine in Rapid Regeneration of Fibrinogen

By E. W. GOODPASTURE

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THIS investigation concerning the activity of the intestine in fibrinogen regeneration followed as a result of two series of experiments described in the preceding paper (Whipple). In the series of "head-thorax circulation" experiments, all the abdominal viscera were excluded from the circulation and a rapid decrease in blood fibrinogen was observed. This fact led to the conclusion that the source of fibrinogen had been removed and the body tissues were rapidly using the circulating fibrinogen. In a second series the liver alone was excluded from the active circulation and no decrease in fibrinogen took place. To explain this, it was suggested that fibrinogen might be supplied to the blood by some means other than liver activity. The fibrinogen might thus be kept at its normal level when the liver was thrown out of function. The most likely source for such a contributing activity seemed to be the intestine.

Evidence has been advanced from time to time in favor of the view that the intestine is a producer of fibrinogen. The results of experimental work upon the subject, however, have been for the most part uncertain, and at times contradictory. Lehmann[2] found blood from the mesenteric vein to be richer in fibrinogen than carotid blood, though venous blood as a whole was poorer in this proteid than arterial blood. This was confirmed by Mathews,[3] who maintained also the intestine to be the chief source of

[1] Aided by a Grant from the Rockefeller Institute.

[2] Lehmann: Quoted from Dastre: *loc. cit. infra.*

[3] Mathews: This journal, 1900, iii, p. 53.

fibrinogen, for it was not re-formed, or was re-formed at a greatly reduced rate after defibrination, if the small and large intestine were removed. His conclusions are based on contradictory and quite inconclusive results of experiments involving extirpation of the intestine of cats and partial defibrination. Dastre [1] included the intestine with the skin and lungs as a producer of fibrinogen. Meek [2] found after an Eck fistula in dogs that fibrinogen is re-formed after defibrination more slowly than normal, and he suggests that intestinal blood furnishes better material than arterial blood for the liver to elaborate into fibrinogen. Doyon and Gautier [3] contend the intestine plays no part in fibrinogen generation; for they detected no delay in fibrinogen reproduction in dogs after total extirpation of the intestine and defibrination of the blood. Such experiments do not, of course, exclude the possibility of fibrinogen generation in the intestine, though evidently the liver can perform this function without aid, but, as our experiments show, at a reduced rate.

An attempt has been made in this series of experiments to study the rate of fibrinogen regeneration in pups completely defibrinated by perfusion.

Method

For the perfusion experiments pups weighing from one to seven pounds were used. Blood for perfusion was shed from normal stock animals, defibrinated by whipping, and used immediately afterward. Since the experiments lasted only three or four hours at most, no attempt was made to conform strictly to aseptic technique. The apparatus consisted of a burette connected by rubber tubing to a tin coil immersed in a water-bath, kept at 40° to 42° C., and connected further by rubber tubing to a canula inserted into a femoral vein. Into the opposite femoral artery an outlet canula was placed.

The pups first received a hypodermic injection of $\frac{1}{16}$ gr. of morphia, which always induced salivation, panting, vomiting, sometimes diarrhoea, and stupor a few minutes afterward. This

[1] Dastre: Archives de physiologie, 1893, v, p. 327.

[2] Meek: This journal, 1912, xxx, p. 161.

[3] Doyon and Gautier: Journal de physiologie et de pathologie générale, 1907, ix, p. 405.

initial dose of morphia was found sufficient to continue anaesthesia throughout the experiment, ether being necessary only during the abdominal operations, in inserting the canulas, and at few brief intervals during the perfusion.

To begin the perfusion, the canulas were opened and the shed blood received into a graduate. The inflow and outflow were kept equal to maintain a constant blood pressure.

Specimens of three to four cubic centimetres were taken at intervals during perfusion until the animal was found to be washed free from fibrinogen, as determined by complete absence of fibrin formation in the specimen.

To obviate interference of anticoagulating substance, fresh spleen extract or glycerin extract of dried brain was added to the specimens, and they were heated to 60° C. fifteen minutes to detect coagulated fibrinogen.

When complete absence of detectable fibrinogen was assured the perfusion was stopped, and samples of blood were drawn every fifteen minutes. If no clot formed in these specimens within the normal time (ten minutes), fresh spleen extract or glycerin extract of dried brain was added.

By observing the quantity and firmness of the clot in given specimens, relative quantities of fibrin can be quite satisfactorily determined where the amounts are very small, i.e., below that necessary to form a clot of sufficient firmness to permit inversion of the test tube. Readings were made at equal intervals after bleeding for all specimens because of clot contraction. One-half inch caliber test tubes were used.

In the earliest detectable amounts fibrin forms small translucent gray threads in which no red corpuscles are enmeshed, then a few pin head sized clots, larger clots, a single clot involving the mass of blood but so soft it does not maintain its shape on inversion of the test tube, a large clot holding its shape but not firm enough to permit inversion, and finally a clot sufficiently firm to adhere to the test tube on inversion.

Normally sufficient fibrinogen is regenerated in fifteen minutes after complete defibrination by perfusion to form a large clot, and in 30 minutes after defibrination a sample of blood will clot firmly enough to permit inversion of the test tube.

Normal Rate of Fibrinogen Regeneration

Pup 20. *Weight* $5\frac{3}{4}$ *lbs. Mongrel; in good condition*

10.15 A.M. Morphine gr. $\frac{1}{16}$.
10.20 Ether anaesthesia. Canulas placed in left femoral artery and right femoral vein.
10.30 Perfusion began.
10.49 Perfused 410 c.c.
10.50 Specimen clotted in normal time forming large lumps.
10.57 Perfused 100 c.c.
10.58 Specimen clotted in normal time forming pea sized lumps, half the size of Specimen I.
11.06 Perfused 100 c.c.
11.07 Specimen formed no clot.
11.21 Specimen clotted in normal time forming pea sized lumps.
11.35 Specimen clotted firmly in normal time.
11.45 Specimen clotted firmly in normal time. Test tube can be inverted without disturbing the clot.

Pup 21. *Weight* $1\frac{3}{4}$ *lbs.*

10.15 Morphia gr. $\frac{1}{16}$.
10.35 Ether anaesthesia. Canulas inserted into right femoral vein and left femoral artery.
11.08 Perfused 200 c.c.
11.10 Specimen I. No clot.
11.40 Specimen II. Large clot, can almost invert test tube.
12.20 Perfused 75 c.c.
12.21 Specimen III. No clot.
12.35 Specimen IV. Small clot.
12.50 Specimen V. Large clot, can almost invert test tube.
1.00 Condition excellent. Respiration good. Skin pink. Pulse strong.

Thus fibrinogen can be reduced quickly to the point where no clotting can be detected, even on the addition of thromboplastin, after which regeneration proceeds rapidly. Several experiments gave quite uniform results.

This is a striking contrast to the delayed appearance and slow increase of clot after ligation of the intestine. The operation is rapidly done. The abdomen is opened under ether and the small and large intestine ligated interruptedly along the fan of

the mesentery, and the abdominal wound closed. No aseptic precautions were used.

Delay in Fibrinogen Regeneration after Ligation of the Intestine

Pup 25. *Weight* $5\frac{3}{4}$ *lbs. Morphine gm.* $\frac{1}{16}$. *Ether anaesthesia.*

11. A.M. 600 c.c. had been perfused. Specimen showed no clot.
11.45 Abdomen opened and intestines ligated. Wound closed.
12.07 Perfused 200 c.c. Specimen showed no clot. Dog in excellent condition. Breathing well. Blood pressure good. Little ether.
12.21 Specimen shows no clot.
12.41 Specimen shows no clot.
1.06 Specimen contains a few pin-head sized lumps.
1.20 Specimen contains large lumps.
1.40 Specimen contains large soft lump involving the mass of blood. Dog in excellent condition.

In this experiment it will be seen there was not enough fibrinogen generated to form an appreciable clot until one hour after the perfusion and then quite minute amounts. In one hour and thirty minutes the amount of clot was not so large as formed in 30 minutes normally.

Pup II. *Weight* $1\frac{1}{2}$ *lbs.*

11.15 A.M. Morphia gr. $\frac{1}{16}$.
11.20 Ether anaesthesia. Abdomen opened and ligature placed around intestine *en masse* including lower portion of duodenum to one half the colon.
12.10 Perfused 82 c.c. Specimen formed a soft clot in normal time.
12.30 Perfused 124 c.c. Specimen showed no clot.
12.40 Specimen formed no clot.
1.00 Specimen formed no clot.
1.30 Specimen formed a soft lump in normal time.
1.45 Specimen formed a soft clot in normal time. Respirations regular. Skin pink. Heart action and blood pressure good.

Blood used for perfusion in this case was taken from a dog suffering from pneumonia, in whose lung areas of consolidation were found at autopsy. Pneumonic blood was used in other cases with poor results, the perfused animals developing a very low blood pressure and dying much sooner than those perfused

with normal blood. The above animal, however, was an exception; during the experiment his condition remained excellent.

Pup III. *Weight* $1\frac{3}{4}$ *lbs.*

11.20 A.M. Morphia gr. $\frac{1}{16}$.
11.30 Ether anaesthesia. Intestines ligated from pylorus to lower colon by interrupted ligatures through the mesenteric fan.
11.45 Perfusion began.
11.58 Perfused 202 c.c. Specimen formed small lumps of clot in normal time.
12.25 Perfused 160 c.c. Specimens formed no clot.
1.00 Specimen formed no clot.
1.25 Specimen formed no clot.
1.55 Specimen formed small lumps of clot.
2.20 Specimen formed large lumps of clot. Pup in good condition. Heart regular. Blood pressure good.

Pup IV. *Weight* 1 *lb.*

4.20 P.M. Morphine gr. $\frac{1}{20}$ in two doses, gr. $\frac{1}{40}$ each 10 minutes apart.
4.40 Pup beginning to become sleepy. Diarrhoea.
4.45 Ether. Canulas introduced into left jugular and right carotid. Abdomen opened and intestine ligated. Respirations began to be weak, and artificial respiration begun.
5.05 Perfusion began.
5.15 Perfused 85 c.c. Specimen clotted softly in normal time. No anaesthesia. Heart beating well.
5.20 Perfused 30 c.c. Specimen formed no clot.
6.00 Perfused 85 c.c. Specimen formed no clot.
6.15 Specimen formed no clot.
6.25 Specimen formed no clot.
6.40 Specimen formed no clot.
7.00 Specimen formed no clot. Heart became weak and the animal died at 7.30. Specimen from heart showed no clot formation. At 8.50 P.M. the 5.20 specimen showed no clot. However, at 9 A.M. the following morning there was a small lump of clot. The subsequent specimens formed no clots, even after the addition of fresh spleen extract.

These experiments suffice to illustrate the constant delay in fibrinogen regeneration after ligation of the intestine and complete defibrination of pups by perfusion.

An interference with the circulation through the liver readily suggests itself as an explanation of this delay. In order to test this the hepatic artery and spleen pedicle were ligated. This procedure cuts off approximately one-half the volume of blood to the liver,[1] and also involves a surgical operation comparable in severity to ligation of the intestine.

Regeneration of Fibrinogen after Ligation of the Hepatic Artery and Spleen Pedicle

Pup 25. *Weight* 6 *lbs.*

10.45 A.M. Morphia gr. $\frac{1}{16}$.

10.50 Ether anaesthesia. Abdomen opened in midline. Hepatic artery ligated at a point just beyond the coeliac axis and again at its recurrent gastric branch. Spleen pedicle ligated. Abdomen closed.

11.23 Perfusion began.

11.37 Perfused 450 c.c. Dog's condition good. Very little ether. Specimen formed firm lump of clot. Cannot invert test tube.

11.43 Perfused 100 c.c. Specimen formed pea sized lumps in normal time.

12.22 Perfused 450 c.c. Specimen formed no clot. Blood pressure good. Respirations rapid. Mucous membranes pink.

12.38 Specimen formed threadlike lumps in normal time.

12.52 Specimen formed jelly-like lump of whole mass of blood.

1.10 Specimen formed firm clot. Can almost invert test tube. Pup in excellent condition. Heart regular. Blood pressure good. Mucous membranes pink.

Autopsy: Hepatic artery ligated in two places. No collaterals found. Spleen pedicle firmly ligated. Other organs normal.

This experiment was repeated with similar result. The rate of fibrinogen regeneration is nearly normal when the arterial and splenic blood is cut off from the liver. There is, however, a perceptible decrease showing that the rate of fibrinogen production is influenced by the volume of blood passing through the liver or by blood pressure relations within the organ, which the arterial blood helps maintain.

To study the influence of the upper and lower halves of the intestine individually, two experiments were performed.

[1] Burton-Opitz: Quarterly journal of physiology, 1910, iii, p. 297, and 1911, *idem*, iv, p. 113.

Regeneration of Fibrinogen after Ligation of one Half the Intestine

Pup 26. *Weight* 2 *lbs.*

10.5 A.M. Morphine gr. $\frac{1}{24}$. Ether.
10.30 Abdomen opened. Upper half of small intestine and spleen pedicle ligated.
10.47 Perfusion began.
11.05 Perfused 200 c.c. Specimen formed large lumps of clot in normal time.
11.45 Perfused 100 c.c. Specimen formed no clot.
12.01 Specimen formed small lumps of clot.
12.16 Specimen formed small lumps of clot.
12.46 Specimen formed large lumps of clot. Pup's condition good. Membranes pink. Blood pressure good.
1.25 Specimen formed small lumps of clot. Pup's condition grew poor after 12.46 bleeding. At 1.25 his blood pressure was low and general condition poor.

Pup 27. *Weight* 2 *lbs.*

10.25 Morphia gr. $\frac{1}{24}$. Ether.
10.40 Abdomen opened, lower half of small intestine and upper half of colon ligated.
10.50 Perfusion began.
11.20 Perfused 200 c.c. Specimen formed lumps of clot in normal time.
11.35 Perfused 100 c.c. Specimen formed no clot.
11.57 Specimen formed small lumps of clot in normal time.
12.15 Specimen formed larger lumps. Blood pressure good. Heart regular.
12.58 Specimen formed no clot. Blood pressure low.
1.30 Specimen formed no clot.

In both these experiments the rate of fibrinogen regeneration is considerably reduced, though in each case there is enough produced within fifteen minutes to form a perceptible clot. There is no great difference in the effect of excluding either half, but the decrease is about what one would expect in view of the greater delay after ligation of the entire intestine. It will also be noticed in the first experiment the last specimen contained a smaller clot than that immediately preceding and the last two specimens in the second experiment formed no clot whatever. This decrease

in the circulating fibrinogen, sometimes complete disappearance, has been noticed several times after ligating the intestine. It is associated with a weakened heart action, lowered blood pressure, and a gradually failing vitality. It may be due to intravascular clotting accompanying the slow circulation.

The complete regeneration of fibrinogen in dogs after total extirpation of the intestine and defibrination was shown by Doyon and Gautier, and is confirmed by the following experiments. Evidently the intestine is not essential to the formation of this proteid.

Regeneration of Fibrinogen after Extirpation of Intestine

Experiment I

10/24/12. *Dog* 12–8. *Weight* 15 *lbs.*

10.00 A.M. Morphia gr. $\frac{1}{4}$, followed in 15 minutes by ether. Operation: Abdomen opened in midline. Common bile duct tied and cut. Vessels of mesentery tied in sections from $\frac{1}{2}$ inch below pylorus to 2 inches above anus. Intestine removed by cutting along fan of mesentery above ligatures. Ends of gut ligated, invaginated, and closed with purse string sutures. Abdomen closed. Time 50 minutes. Within 15 minutes canulas were inserted into right femoral vein and left femoral artery.

11.34 Bled 50 c.c. into oxalate. Reinjected defibrinated blood, from D. 12 50 c.c.

11.40 Bled 50 c.c. defibrinated, injected 40 c.c.

11.50 " 50 c.c. " " 50 c.c.

12.00 " 50 c.c. " " 40 c.c.

12.05 " 50 c.c. into oxalate " 40 c.c.

Vessels ligated.

The last bleeding was slow due to clot in canula and blood clotted in oxalate before fibrinogen estimation could be made. All shed blood clotted firmly in 2 minutes. Dog recovered from anaesthesia slowly.

12.30 Morphia gr. $\frac{1}{8}$.

3 P.M. Sleeping quietly.

5.10 Sleeps most of time. Occasionally arouses.

8.00 Found standing beside box. Very weak. Morphia gr. $\frac{1}{8}$.

10/25/12. 9 A.M. Sleeping quietly on mat. Raises head when aroused. Coarse rales on expiration. Temperature 32.5° C.

11.30 Under cocaine a canula was inserted into right femoral artery and 50 c.c. blood drawn into oxalate.

2.00 P.M. Dead.

The oxalate specimens were drawn into 5 c.c. 1 per cent sodium oxalate, up to 50 c.c. After centrifuging, the specimens possessed about the same proportion of plasma and corpuscles. 23 c.c. clear plasma were recovered in each case. In specimen 2, in spite of the oxalate a small amount of fibrin formed. 20 c.c. plasma from each specimen were heated to 60° 15 minutes, centrifuged, washed twice with cold, once with warm water, then with alcohol and ether. Dried to constant weight.

Fibrinogen before defibrination	24 hours after defibrination
0.3670 gm. per 100 c.c.	0.4760 per 100 c.c.

11/26/12. *Dog* 12–15. *Male, fox terrier. Weight* 16 *lbs.*

5 P.M. Ether anaesthesia.

5.04 Bled 120 c.c. defibrinated, reinjected 5.09, 105 c.c.
5.12 " 100 c.c. " " 5.17, 110 c.c.
5.21 " 100 c.c. " " 5.27, 100 c.c.
5.30 " 100 c.c. " " 5.37, 100 c.c.
5.41 " 100 c.c. " " 5.46, 100 c.c.

Vessels ligated.

Recovered from anaesthetic readily.

11/27/12. 9 A.M. Dog well and active.

10.30 Ether.

Abdomen opened in midline, small and large intestine resected. Wound closed.

12.06 Bled into oxalate 50 c.c. Reinjected, defibrinated blood from D. 12–3 12.08, 50 c.c.
12.09 Bled 50 c.c. defibrinated, reinjected 12.13, 50 c.c.
12.15 " 50 c.c. " " 12.17, 50 c.c.
12.20 " 50 c.c. " " 12.22, 50 c.c.
12.24 " 50 c.c. " " 12.26, 50 c.c.
12.30 " 50 c.c. into oxalate, reinjected (D. 12–3) 75 c.c.

Vessels ligated. Dog recovered from anaesthetic slowly. Dazed.

1.00 P.M. Morphia gr. $\frac{1}{8}$. Vomiting. Slept quietly all afternoon.

6.00 Morphia gr. $\frac{1}{8}$.

8.00 Very drowsy.

8.15 Bled without anaesthetic and painlessly 50 c.c. into oxalate. Bled freely.

11/28/12. 9 A.M. Found dead in cage.

Dog 12–15. *Fibrinogen estimation*

Immediately after resection of intestines	After defibrination	8 hrs. later
0.3165 gm. per 100 c.c.	0.1595 gm.	0.3195

EXPERIMENT III

11/12/1. *Dog* 12–14. *Weight* 16 *lbs.*

5.30 Ether. Canulas in right femoral vein and left femoral artery.
5.43 Bled 80 c.c. defibrinated, reinjected 5.30, 65 c.c.
5.55 " 95 c.c. " " 6.00, 95 c.c.
6.08 " 90 c.c. " " 6.13, 90 c.c.
6.17 " 95 c.c. " " 6.21, 105 c.c.
6.25 " 90 c.c. " " 6.30, 90 c.c.
Vessels ligated.
Dog recovered readily from anaesthesia.
11/13/12. 9 A.M. Dog looks rather weak.
10 A.M. Ether. Operation: Extirpation of intestine.
11.51 Bled into oxalate 50 c.c. Reinjected defibrinated blood from D. 12–3 11.55, 50 c.c.
11.57 Bled 50 c.c. defibrinated, reinjected 12.05, 50 c.c.
12.08 " 50 c.c. " " 12.10, 40 c.c.
12.13 " 50 c.c. " " 12.15, 50 c.c.
12.17 " 50 c.c. " " 12.18, 50 c.c.
12.21 " 50 c.c. (oxalate) " 12.24, 45 c.c.
12.30 Morphia gr. $\frac{1}{8}$. Dog not recovering readily from anaesthesia. Great salivation.
2.00 P.M. Dog lying on mat. Respirations very deep.
3.15 Unconscious. Barking expiration.
3.20 Canula in carotid. Bled 50 c.c. into oxalate.

Fibrinogen immediately after operation.	After defibrin.	3 hrs. later
0.3540 per 100 cc.	0.1440	0.2140

Fibrinogen in 20 c.c. plasma was estimated in each case. After centrifuging, the proportion of plasma and corpuscles was about the same for each. 24 c.c. clear plasma were recovered from each specimen.

In the first experiment, 24 hours after extirpation of the intestine and defibrination the fibrinogen was above normal. In the second and third experiments a preliminary defibrination was

done with the idea of perhaps exhausting a reserve supply of fibrinogen. In such an event it was thought the regeneration after extirpation of the intestine and a second defibrination might be retarded. Such does not seem to be the case. Within eight hours the fibrinogen returned to normal.

Chloroform Poisoning and Fibrinogen Regeneration

The method of complete defibrination by perfusion offered an excellent means to determine whether the fall in fibrinogen after chloroform poisoning be due to a total suppression of fibrinogen formation and a using up of the circulating proteid, or whether there be a decrease in fibrinogen producing power concomitant with and proportional to the fall in fibrinogen. The following experiments were undertaken with this purpose in mind:

Rate of Regeneration of Fibrinogen after Chloroform Anaesthesia

Pup 28. *Weight* $4\frac{3}{4}$ *lbs.*

4/19/13. 3 P.M. Light chloroform anaesthesia for $1\frac{1}{2}$ hrs.
4/20/13. 9 A.M. Dog appears well.
11.20 Administered hypodermically morphia (gr. $\frac{1}{16}$).
11.30 Canula placed in right femoral vein and left femoral artery under ether anaesthesia.
11.49 Perfused 200 c.c.
11.50 Bled. Specimen I. Pea sized lumps.
12.03 Perfused 150 c.c.
12.04 Bled. Specimen II. No clots
12.07 " Specimen III. No clots.
12.15 " Specimen IV. No clots.
12.35 " Specimen V. No clots.
12.50 " Specimen VI. No clot.
1.05 " Specimen VII. No clot.
Pulse regular and full.
1.55 Bled. Specimen VIII. Large soft lump involving entire mass of blood.
Vessels were ligated after the last bleeding and the animal placed in a cage.
At 4 P.M. he was found dead and was autopsied at once. The liver showed central necrosis, which on microscopic examination was

found to involve about $\frac{3}{5}$ of the lobule. The blood first drawn clotted in the normal time forming soft lumps. At room temperature no fibrinolysis had taken place at the end of 24 hrs.

The fibrinogen content of this animal's blood was very low as is indicated by the relatively small quantity of perfused blood necessary to completely defibrinate it. There was also a marked delay in the rate of fibrinogen regeneration. At the end of one hour no perceptible clot formed in the specimen and after two hours only about as much as normally appears in one-half hour.

The Rate of Fibrinogen Regeneration immediately after Chloroform Anaesthesia for One Hour

Pup 29. *Weight* 3 *lbs.*

11.15 Light chloroform anaesthesia for 1 hr.
12.15 Morphia (hypo.) gr. $\frac{1}{16}$ administered.
12.30 Canulas placed in femoral artery and vein.
1.07 Perfused 300 c.c.
1.08 Specimen I. Firm clot. Cannot invert tube.
1.18 Specimen II. Large soft lump.
1.29 Perfused 75 c.c.
1.30 Bled. Specimen III. Pin-head sized lump. Condition good; has had no anaesthesia since operation; under morphia; can be aroused when disturbed.
1.45 Bled. Specimen IV. Pea sized lump.
2.00 Bled. Specimen V. Soft clot of entire mass of blood.
2.15 Bled. Specimen VI. Soft clot.
2.30 Bled. Specimen VII. Firmer clot.
3.30 Bled. Specimen VIII. Firm clot, but cannot invert test tube. Dog in good condition. Pulse regular and full. Killed with ether.

Autopsy: Liver is pale and mucous membranes of intestines slightly congested. The specimens of blood clotted very slowly. The readings above given were made at 5.30 P.M. after maximum clotting had taken place.

This animal was not completely defibrinated, yet specimen III contained only a minimal amount of fibrin and the subsequent bleedings formed clots progressively larger. Although the regeneration of fibrinogen was much more rapid than in the dog, 20 hours after chloroform, the rate was less than normal. The clot

obtained after two hours contained less fibrin than is normally present in one hour after complete defibrination. One may assume from this that though the liver is injured immediately by chloroform, the injury is a progressive one, reaching its maximum after about 24 hours.

The lowered fibrinogen equilibrium corresponding to a contemporaneous fall in fibrinogen production suggests that there is a rapid utilization by the body of its circulating fibrinogen, or that the presence of the injured liver cells (hyaline necrosis) in some way depletes the plasma of its fibrinogen.

Discussion

The mechanism for maintaining the fibrinogen equilibrium is capable of an immediate response to a tremendous demand. So effective is the response that within a few hours after defibrination the fibrinogen content of the blood will rise from almost zero to normal or even above. The power of rapid reproduction, normally prevailing, lends significance to the marked delay in fibrinogen formation after exclusion of the intestine. This delay is not due to a decrease in the volume of blood supplying the liver. It may best be explained by assuming that the intestine is a contributing factor in the normal production of fibrinogen. It is not clear whether the intestine actually elaborates fibrinogen or contributes something to the liver which facilitates the production of it. The absence of a decrease in fibrinogen, when only the liver is excluded from the circulation, supports the view that the intestine supplies it directly to the blood. Some experiments described by Meek do not uphold this view. By excluding the liver from the circulation and partially defibrinating dogs, he observed a diminution in the remaining fibrinogen. In one case out of the three the blood was found to be incoagulable from lack of fibrinogen two hours after defibrination. We have observed in several instances with the liver circulation intact a decrease or total disappearance of fibrinogen from the blood. This occurred in pups whose blood pressure remained very low after partial defibrination. Meek's animals underwent a severe operation and he does not state their condition during the experiment. The explanation

is perhaps warranted that the decrease in fibrinogen which he observed was due to low blood pressure and retarded circulation. Such a condition may not only prevent fibrinogen formation, but may diminish fibrinogen present in the blood, perhaps by intravascular clotting.

It is quite evident, on the other hand, that intestinal blood is not necessary for the formation of fibrinogen by the liver. This is shown by the regeneration of fibrinogen in dogs whose intestine has been completely extirpated. This fact, too, would seem to indicate that the delay in fibrinogen formation after the intestine is excluded is due rather to a suppression of a normal output of this substance by the intestine than to the absence of something which facilitates its production by the liver.

Bohr stated that after exclusion of the intestine the blood became incoagulable. Mathews (*loc. cit.*) confirmed this, but found the incoagulability was not due to absence of fibrinogen. In our perfusion experiments specimens taken at frequent intervals during the perfusion have nearly always clotted within the normal time, one to seven minutes. There has been no marked delay at any time except in the second chloroform experiment, where the process of clotting extended over a considerable period, one hour or more. One might rather expect the introduction of defibrinated blood, rich in thrombin, to be followed by an antithrombin excess.

The experiments with chloroformed pups show an immediate decrease in the power of these animals to produce fibrinogen. The liver injury is progressive and is accompanied by a proportionate diminution in fibrinogen generative power. This does not explain the rapid decrease in circulating fibrinogen after severe chloroform poisoning. It may be assumed that the liver necrosis in some way causes an abnormal using up of fibrinogen.

Summary

1. Pups rapidly reproduce fibrinogen after complete defibrination by perfusion. Thirty minutes after defibrination a firm clot forms in blood specimens.

2. Ligation of the hepatic artery and spleen pedicle causes a

slight but noticeable reduction in the rate of fibrinogen regeneration after complete defibrination.

3. Ligation of the intestine causes a *marked delay* in fibrinogen reproduction after complete defibrination. Hardly as much fibrinogen is produced two hours after defibrination as in one-half hour normally.

4. After total extirpation of the intestine in adult dogs the fibrinogen returns to normal within eight hours.

5. Chloroform anaesthesia for one hour causes an immediate decrease in fibrinogen regeneration after defibrination. Twenty hours after the anaesthesia the delay in fibrinogen production is more marked.

These facts have led to the conclusions that: (1) Normal fibrinogen production is a result of the combined activity of the liver and the intestine; (2) The intestine is not essential to fibrinogen regeneration, but is an important contributing factor in its rapid formation.

ON THE SECRETION OF GASTRIC JUICE IN THE CAT

By A. J. CARLSON, J. S. ORR, and W. F. BRINKMAN

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IN the investigation of the condition of the digestive tract in parathyroid tetany by the X ray method of Cannon, it was usually necessary to feed the animals forcibly, as anorexia nearly always accompanies the tetany.[1] Presumably, feeding an animal forcibly excludes appetite secretion of gastric juice. Cannon has shown that the intensity of the gastric digestive movements is correlated with the state of gastric digestion. Absence of psychic gastric juice would therefore appear to be a serious source of error, and the attempt was made to minimize this error by adding proteoses and peptones to the meat, so that the secretion initiated through local mechanisms would start as soon as the food reached the stomach. It was felt, however, that the influence of forced feeding on the secretion of gastric juice should be determined by direct experiments on normal animals.

Most of the work was done on cats with a gastric pouch isolated according to Pawlow. Oesophagotomy was made in one cat with a Pawlow pouch and in two cats with gastric fistula. To avoid erosion of the wound by gastric juice, and infection, it proved expedient to insert a rubber tube in the pouch and stitch it on either side so as to hold it in place. The entire wound was then covered by a sterile gauze secured to the intact skin by collodion. In this way the juice was drained away from the wound and skin infection prevented. This bandage was left on for four or five days when primary intention had taken place. It is quite essential in cats to drain the juice away from the abdominal wall during the feeding and digesting period, so as to prevent digestion of the surrounding tissue.

[1] Carlson: This journal, 1912, xxx, p. 309.

I. Appetite Secretion of the Gastric Juice

The results on five typical animals are summarized in Table I. It will be seen that the course of appetite secretion in the cat is practically identical with that in the dog as shown by Pawlow and his co-workers. The secretion is greatest in quantity during the first hour, but persists with gradually decreasing rate for two to three hours. The actual quantity secreted, other conditions being the same, depends on the size of the pouch. Cat 27, with gastric fistula and divided oesophagus, secreted nearly 9 c.c. of juice during the three hours after drinking milk for five minutes (sham feeding). Cat 28 secreted 13 c.c. of juice in three hours while seeing and smelling meat. It would therefore seem that the accessory stomachs of our animals contained on the average a little less than $\frac{1}{10}$ of the total gastric glands.

We invite particular attention to Cat No. 15. Sham feeding of milk and sham drinking of water yielded practically equal quantities of appetite gastric juice from the pouch.

II. The Secretion of Gastric Juice after Forced Feeding

In order to secure data that may reveal approximately the quantity of appetite gastric juice secreted during a normal meal it is necessary (1) that the animal be actually hungry at the time he is being fed forcibly, and (2) the food given forcibly should contain the same quantity of secretagogues as the food taken voluntarily. The presence of hunger and appetite indicates a certain degree of tonus of the stomach musculature and nervous tissue as well as a certain degree of rest of the gastric glands. The only way to meet these two conditions is to give unpalatable food to the hungry animals. Minced cat muscle probably contains the same quantity and kind of secretagogues as minced ox muscle. All hungry cats eat lean meat, and to our surprise most of the cats after a 24 hour fast eat cat muscle quite as greedily as butcher's meat. Some of the cats, however, refused cat muscle. Cat No. 20 ate calves' liver with great relish, but would not touch cat muscle or cat's liver. The summary of three parallel experiments on this cat with calves' liver

and cat's liver is given in Table II. The forced feeding was done by placing the minced liver on the back part of the tongue. In the process of forced feeding the animals struggle a great deal unless bundled up in a blanket or large towel. If this is done the animal lies fairly quiet and does not offer much resistance. It is clear from Table II that the rate and duration of gastric secretion after feeding cat's liver forcibly are identical with the gastric secretion after eating calves' liver voluntarily. The gastric secretion of the same cat following the voluntary eating of 50 c.c. of milk is summarized for the purpose of comparison. When the cat eats milk voluntarily there is at least some secretion of appetite juice, but the milk contains less secretagogues than raw meat or liver, in addition to the local inhibitory action of the milk fat. The scanty total secretion following the voluntary ingestion of 50 c.c. of milk as compared with the secretion following the forcible feeding of 50 gr. cat's liver points to the conclusion that the nature of the food (i.e., the quantity of secretagogues) is much more important than psychic secretion in determining the total quantity of gastric juice secreted after a meal.

The results on other cats are summarized in Table III, only the total quantity of gastric juice for equal periods being given. We wish to call particular attention to Cat No. 14. This animal ate raw meat with apparent relish, but refused to touch liver. This was the only cat that refused fresh liver from the butcher shop. Accordingly the tests on this cat were made with minced raw beefsteak and minced calves' liver. The average of five experiments with each shows that the quantity and quality of the gastric juices in the two series are identical.

Milk, whether ingested voluntarily or given forcibly, yields practically identical quantities and concentrations of gastric juice. None of the cats would eat bread voluntarily. When given forcibly in the same quantity as meat or the liver, bread always yielded a very small quantity of gastric juice of low acidity. According to Pawlow's results on dogs the gastric juice secreted on a bread meal has a higher acidity than that secreted after eating meat. Our results indicate on the other hand that the acidity of the gastric juice is mainly a question

of rate of secretion — slow secretion allowing time for neutralization by the alkaline mucus secretion.

How are these results to be reconciled with the facts of appetite secretion of gastric juice? In the first place it is not likely that forcible feeding of unpalatable food initiates psychic secretion of gastric juice even when the animal is hungry. But the following consideration probably explains the discrepancy. The striking experiments with sham feeding of dogs and teasing hungry dogs with food are important in working out the mechanism of these reflexes, but they do not show the relative importance of the appetite secretion in normal feeding. In normal feeding the sensation of hunger and appetite is soon replaced by that of satiety, and it is not likely that psychic secretion persists beyond that point. This cannot be compared to the effects of persistent stimulation by sham feeding or teasing with food with unappeased appetite and absence of satiety. Provided the digestive tract is in the condition of hunger and the material placed in the stomach contains an abundance of secretagogues, the presence or absence of psychic gastric juice is of slight importance. The same is indicated by the efficient gastric digestion in animals with section of both vagi in the chest.

III. The Psychic Secretion of Gastric Juice from Drinking Water when Thirsty

The relatively scanty secretion of gastric juice after voluntarily eating milk suggested control experiments with drinking water on the part of the thirsty animal. We wish to refer again to Cat No. 15, Table I. The cat was thirsty, but the water drinking was sham, none of the water entering the stomach. The secretion of gastric juice following this act must therefore be a reflex initiated by the water in the mouth and pharynx, unless we assume that the water drinking caused the animal to think of palatable food. This is the only animal tested with the method of sham drinking. But numerous tests were made with the thirsty animals actually drinking the water. In this case other factors probably enter, such as the local action of water in the stomach, the washing into the intestine and subsequent absorption of traces of secretagogues in the stomach, and

the actual dilution of the blood. Our results show that drinking water on the part of the thirsty animal nearly always causes secretion of gastric juice. As an example, we submit a summary of the tests on Cat No. 27. This cat had a relatively large stomach pouch and was in excellent condition.

	Gastric juice	Acidity		
	quantity (3 hr.)	Free	Combined	Total
Milk (50 c.c., 4 tests)	3.46 c.c.	0.36	0.18	0.55%
Water (50 c.c., 8 tests)	1.0 c.c.	0.05	0.19	0.25%

The secretion is always greatest the first hour after the water drinking, and the secretion practically ceases after two or three hours. The following figures from individual tests for Cat 27 may be cited in illustration:

	1st hour	2d hour	3d hour
Gastric juice (c.c.) after drinking water	0.6	0.4	0.2
	0.8	0.4	0.2
	0.5	0.4	0.2

It is clear, therefore, that in the thirsty cat drinking water causes secretion of gastric juice. Pawlow and his co-workers (Chigin, Jürgens, Ssanozki) regard water in the stomach as a direct (chemical) stimulus to gastric secretion. Edkins[1] seems to have shown. on the other hand, that water or rather physiological salt solution in the stomach does not stimulate the gastric glands. The negative results of Edkins might be due to the fact that his animals were under deep anaesthesia and the stomach subjected to severe manipulation. It is also to be noted that in Edkin's experiments the water or salt solution

[1] Edkins: Journal of physiology, 1906, xxxiv, p. 133.

did not enter the intestines. It was all retained in the stomach. This was not the case in Pawlow's experiments. It is well known that practically all the water drunk on an empty stomach is passed into the intestines within a few minutes. It is not likely that water remaining in the empty stomach scarcely more than five minutes can by direct (chemical) stimulation of the gastric glands or local nerves induce a secretion lasting two hours or more. Pawlow has shown in the dog that the latent period of gastric glands is about five minutes. The water is therefore already in the intestine before the stomach actually begins to secrete. It is more likely that the drinking of water stimulates local secretory mechanism in a more round about way. If the animal is thirsty the water drinking causes "psychic" secretion. And it is probable that the water washes traces of gastric secretagogues or secretins into the intestine, where they are absorbed and act on the gastric glands via the blood. It is probable that traces of secretagogues or secretins are ordinarily present in the empty stomach. Some gastric juice is nearly always present, fragments of bone and muscle fibres, etc., are frequently present. But even in the absence of these food remnants, it is likely that the pepsin-hydrochloric acid digestion of mucin and the proteins of the gastric juice itself yields traces of secretagogues. It is also probable that the dilution of the blood that results from drinking water favors the gastric secretion. These suggestions are supported by the following experiments. It was found almost invariably that following a meal of meat or liver the secretion of gastric juice is most copious the first hour, and the secretion rate falls gradually until it ceases entirely at the end of the seventh to the ninth hour, that is, it then reaches the level of the continued spontaneous secretion of the empty stomach. Now if an animal is kept fairly thirsty when fed, and then allowed to drink water at the end of the second, third, or fourth hour after feeding, the rate of gastric secretion during the hour following the water drinking becomes as great or greater than during the first hour after feeding. Four typical experiments may be cited as illustrations:

Secretion of Gastric Juice (c.c.) per Hour after Voluntary Feeding

Cat 12	Cat 12	Cat 14	Cat 24
75 gr. liver	75 gr. liver	50 gr. meat	50 gr. liver
1.0	0.9	.8	1.1
.7	0.6	.5	.6
.5	drank water	.8	.7
.5	1.2	.8	.7
drank water	.6	drank water	drank water
1.8	.4	1.0	1.1
1.0		.6	.7
.6		.3	.5
.3		.1	.4
.2			

As these animals were actually thirsty, it is probable that the increased secretion was partly psychic. This factor is at least not eliminated in these experiments. But the increase is usually too great to be accounted for by this factor alone. We think that the main factor is the facilitation of the passage of the chyme into the intestine and the absorption of secretins from the intestine. It did not occur to us until it was too late, to test the factor of blood dilution by direct dilution of the blood. These experiments certainly demonstrate the favorable action on gastric secretion of water taken with or after the meal.

The psychic secretion of gastric juice following the drinking of water on the part of the thirsty animal is probably due to a close linkage of the cerebral processes of hunger and thirst, as well as the cerebral processes of satiety or satisfaction following eating or drinking. But this must remain a mere suggestion until the focal point or "centre" for these sensations is more definitely located.

TABLE I

APPETITE SECRETION OF GASTRIC JUICE IN THE CAT (C.C. PER HOUR)

Hour	Pawlow stomach. Cats seeing meat, milk, chalk water		Cat No. 15. Pawlow stomach and oesophagotomy		Gastric fistula and oesophagotomy	
	Cat No. 12 10 exp.	Cat No. 20 6 exp.	Drinking milk 5 min. 2 exp.	Drinking water 5 min. 2 exp.	Cat No. 27 drinking milk 5 m. 2 exp.	Cat No. 28 seeing meat after being without food 48 hr.
1.	.5	.4	.3	.3	3.4 c.c.	6.1 c.c.
2.	.2	.3	.2	.2	2.9 c.c.	4.3 c.c.
3.	.1	.1	.1	.0	2.4 c.c.	2.4 c.c.
Total	0.8 c.c.	0.8 c.c.	0.6 c.c.	0.5 c.c.	8.7 c.c.	12.8 c.c.

TABLE II

CAT NO. 20. STOMACH POUCH ACCORDING TO PAWLOW. RATE OF SECRETION OF GASTRIC JUICE DURING THE FIRST NINE HOURS AFTER EATING WITH APPETITE, AND AFTER BEING FED UNPALATABLE FOOD (CAT LIVER) FORCIBLY WHEN HUNGRY

With appetite 50 gr. liver (3 exper.)	Forced feeding (cat hungry) 50 gr. cat liver (3 exper.)	With appetite 50 c.c. milk (3 exper).
1.6	1.3	.6
1.4	1.5	.4
1.0	1.0	.3
.6	.7	.2
.5	.7	.2
.5	.6	.2
.5	.6	.2
.6	.5	.1
.4	.3	.0
7.1 c.c.	7.2 c.c.	2.2 c.c.

TABLE III

CATS WITH STOMACH POUCH ISOLATED ACCORDING TO PAWLOW, SECRETION OF GASTRIC JUICE AFTER EATING SPONTANEOUSLY AND AFTER FORCED FEEDING

Animal	Food	No. of expr.	Time, hours	Gastric juice	
				Quantity (c.c.)	Acidity (total)
Cat 12	25 gr. liver voluntarily	6	9	3.20	.39%
	25 c.c. milk voluntarily.....	2	9	2.10	.23%
	25 gr. bread forcibly	3	4	1.60	.26%
Cat 14	25 gr. raw meat voluntarily..	5	9	3.05	.41%
	25 gr. liver forcibly	5	9	3.10	.41%
	25 gr. bread forcibly	2	4	0.75	.28%
	25 gr. tomato pulp forcibly ..	2	4	0.80	.31%
Cat 20	50 gr. liver voluntarily	3	9	7.1	.48%
	50 gr. cat liver forcibly.....	3	9	7.2	.44%
	50 c.c. milk voluntarily.....	3	8	2.2	.25%
Cat 24	50 gr. liver voluntarily	5	9	5.10	.48%
	50 c.c. milk voluntarily.....	3	6	1.35	.21%
	50 c.c. milk forcibly.....	3	6	1.05	.17%
Cat 25	25 gr. liver forcibly	2	9	3.70	.41%

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

VIII. The Hunger Contractions of the Empty Stomach During Prolonged Starvation (Man, Dog)

By A. J. CARLSON

[*From the Hull Physiological Laboratory of the University of Chicago*]

THE experimental procedure followed in these starvation experiments on the dogs were identical with that described in a previous communication. All the dogs were provided with a gastric fistula, so that none of the records of the hunger contractions were taken via the esophagus.

Mr. V. cannot very well be employed for observations involving prolonged starvation, because his hunger contractions become very strong and uncomfortable even within ten to fifteen hours after eating. There is a slow but more or less continuous secretion of gastric juice in the empty stomach and it is practically impossible to prevent leakage of some of this gastric juice around the rubber tube in the fistula, especially when the empty stomach is in hunger tetanus. The escaping gastric juice corrodes and, as he says, "burns" the skin around the fistula. Prolonged starvation is therefore so uncomfortable to Mr. V. that I did not feel justified to subject him to it, even though he expressed his willingness. The experiment was therefore carried out on the writer (age 38) and on one assistant, Mr. J. H. L. (age 22). Mr. L. is a graduate student in Physiology and Pathology, and trained in research.

As recording balloon in the stomach we used a best quality rubber condom adjusted to a flexible rubber tubing of 3–5 mm diameter. This size tubing is sufficiently large for rapid passage of air so as to give accurate records of the stomach contractions. Other things being equal the smaller and more flexible the rubber tube the less disturbance and inconvenience in the mouth

and pharynx in the way of salivation, gagging, etc. The ordinary stomach tubes are too large and not flexible enough. By means of such balloons and rubber tube connections records have been taken of the gastric hunger contractions of seven men to date. Three of these men swallowed the balloon and tube practically without gagging or salivation, and normal record of the gastric tonus and hunger contractions for 2 to 4 hours were secured from them at the very first trial. Two of the men succeeded in overcoming the gagging and salivation after three or four days trial, while in the case of the writer and one of the assistants, the gagging was so annoying that recourse was had to light cocainizing of the pharynx for the first experiment. But this was done before we had discovered the importance of a small and flexible rubber tube, and the further fact that the balloon and tubes must be *swallowed*, not *pushed* through the esophagus. Our initial trouble was mainly due to our following the ordinary technique of passing a stomach tube, that is, assist the swallowing by *pushing* on the tube. This invariably results in gagging. If the balloon and tube is simply *swallowed slowly* and aided with a few sips of water many persons can do it at the first or second attempt, and without the least gagging or much inconvenience. The most convenient way to hold the tube in the mouth is slipping it between the jaws behind the last molars and letting it lie between the cheek and the teeth. In this way the tongue is free, and ordinary conversation can be carried out. The method is so simple and easily mastered that it can be employed in ordinary laboratory instruction. The gastric contractions were recorded by means of bromoform or chloroform manometers, as in the case of previous work on Mr. V.

Records of the hunger contractions were taken with the men standing, sitting and lying down. There are minor variations in the tracings depending on the position of the subject. This is evidently due to the variations in the position of the viscera. The best records are secured with the subject lying on the back, and all muscles relaxed as much as possible. Under these conditions the viscera do not press on the stomach, and the tension of the abdominal muscles is diminished.

During the five days starvation period the two men continued their usual work during the day, and records of the stomach tonus and hunger contractions were taken at varying intervals. During the night continuous records were taken beginning 8 to 9 P.M. and ending 5 to 6 A.M. Neither the writer nor Mr. L. found much difficulty in sleeping for 6 to 8 hours every night with balloon and tube in the stomach. The room was kept dark except for a feeble light focussed on the drum so as to enable the assistant to take care of the recording. And the assistant took special care to keep everything as quiet as possible. One assistant took care of the recording from 8 A.M. to 2 P.M. and a second assistant from 2 to 6 A.M. The time 6 to 8 A.M. and 6 to 8 P.M. was usually spent in walking in the park; in any event, outside the laboratory.

I. Results on Man

1. *The Objective Phenomena. The Hunger Contractions*

Before beginning the starvation period observations on the gastric hunger contractions of the writer were made every second or third day for three weeks. These observations were usually made in the morning after dispensing with breakfast, or else during the middle of the day, thus dispensing with lunch. No observations were made during night or sleep. These records are quite uniform in character, and represent the degree of hunger contractions exhibited by the writer's stomach 6 to 15 hours after a meal. These periods of hunger contractions are essentially similar to those of Mr. V. already reported in detail, with this important difference, that in my own case the hunger periods never culminated in the incomplete tetanus so characteristic of the stomach of Mr. V. A typical culmination of a hunger period of the writer is given in Fig. 1A.

We now wish to direct the reader's attention to the following:

Summary of the Observations During the Starvation Period of A. J. C.

June 29. — No breakfast. First hunger period began gradually at 8:45 A.M. lasting for about 45 minutes; 16 strong contractions

in 30 minutes. A second period ended at 11:30 lasting about 30 minutes. There were 22 strong contractions in 30 minutes.

Last meal. — Two slices of toast and a glass of milk at 12:30 P.M. Body weight 74 K.; no observations during the night.

June 30, A.M. — 11:50–12, 20 fairly strong contractions.
12:20–1:50, quiescence.
P.M. — 1:50–2:30, 18 fairly strong contractions.
2:30–4:30, quiescence.
Interruption
9:15–10:00, 22 strong contractions.
10:00–11:10, fairly quiescent.
11:10–11:50, continuous feeble contractions.
11:50–12:30, 36 strong contractions.

July 1, A.M. — 12:30–12:40, quiescence.
12:40–1:20, continuous feeble contractions.
1:20–2:25, 45 strong contractions.
2:25–2:50, continuous feeble contractions.
2:50–3:30, 27 strong contractions.
3:30–4:00, quiescence.
4:00–4:30, continuous feeble contractions.
4:30–5:20, 26 strong contractions.
Interruption
8:45–9:55, 43 strong contractions.
10:20–12:20, contractions all the time, but feeble.
P.M. — 12:20–1:00, 19 strong contractions.
Interruption
3:35–4:00, 20 fairly strong contractions.
Interruption
8:35–9:25, 37 strong contractions.
9:25–11:20, continuous fairly strong contractions.
11:20–12:25, 47 very strong contractions.

July 2, A.M. — 12:25–12:50, fairly quiescent.
12:50–2:35, continuous fairly strong contractions (60 con.).
2:35–3:30, fairly quiescent.
3:30–4:50, 70 strong contractions ending in tetanus (4 min.).
Interruption
6:30–7:40, quiescence.
7:40–8:40, 33 strong contractions.
Interruption

10: 25–11: 15, 29 strong contractions.

Interruption

1: 00–3: 00, continuous fairly strong contractions, stronger towards the end.

Interruption

8: 45–9: 00, 22 strong contractions.
9: 00–9: 50, continuous feeble contractions.
9: 50–10: 30, 27 strong contractions.
10: 30–11: 30, continuous fairly strong contractions.
11: 30–12: 30, 34 strong contractions.

July 3, A.M. — 12: 30–2: 25, continuous fairly strong contractions.
2: 25–3: 40, 60 strong contractions ending in incomplete tetanus (5 min.).
3: 40–4: 05, continuous feeble contractions.
4: 05–5: 00, 42 strong contractions.

Interruption

8: 30–9: 25, 30 strong (not maximum) contractions.
11: 25–1: 00, continuous fairly strong contractions.
1: 00–1: 40, 30 strong contractions.

Interruption

4: 45–5: 15, continuous feeble contractions.

Interruption

9: 00–9: 45, 38 strong contractions.
9: 45–11: 20, continuous feeble contractions.
11: 20–12: 10, 39 strong contractions.

July 4, A.M. — 12: 10–1: 10, continuous feeble contractions.
1: 10–2: 35, 60 strong contractions.
2: 35–3: 40, fairly quiescent.
3: 40–5: 40, 50 strong contractions.

End of Experiment. Body Weight, 69.8 K. Loss of Body Weight, 4.2 K.

Confining our attention for the present to the objective phenomena, i.e., the gastric tonus and the hunger contractions, the following facts are apparent:

1. There is no decrease in the gastric tonus and the hunger contractions, but, on the contrary, an increase, especially in the tonus, and in the frequency of the hunger periods. An increase in the intensity of the hunger contractions is also evidenced in

the appearance of the incomplete hunger tetanus on the fourth and fifth days of starvation (Fig. 1B).

2. The gastric hunger contractions are at least as frequent and intense during sleep at night as during the waking state. In this series the hunger periods appear even to be augmented during sleep, but that may be due to the more frequent inter-

FIGURE 1. (Four-ninths the original size.) Records of the contractions of the empty stomach of A. J. C. (age 38). Bromoform manometer. *A*, final ten minutes of a typical period of hunger contractions ten hours after a meal. *B*, final ten minutes of a typical hunger period after five days starvation. Note in tracing *B* the prolonged period of incomplete tetanus at the culmination of the hunger period, and the reappearance of a feeble 20-seconds rhythm immediately following the cessation of the period of strong hunger contractions. Showing the increase in the tonus and the hunger contractions of the empty stomach during prolonged starvation.

ruptions and to cerebral or psychic inhibitions in the daytime. The following summary of the records during the four nights that observations were made shows the stomach of the writer in strong hunger contractions practically half of the time, which was not the case during the day.

Gastric Hunger Contractions During Sleep at Night

June 30 to July 1: 8 hours record — 5 periods of strong contractions; 169 individual contractions in 4 hours.

July 1 to July 2: 8 hours record — 4 periods of strong contractions; 204 individual contractions in 4 hours and 20 min.

July 2 to July 3: 8 hours 15 minutes record — 5 periods of contractions; 188 individual contractions in 4 hours 5 min.

July 3 to July 4: 8 hours record — 4 periods of strong contractions; 187 strong contractions in $3\frac{1}{2}$ hours.

3. There was a continuous but probably scanty secretion of gastric juice during the entire hunger period, as the balloon on being withdrawn from the stomach always tasted acid and gave the acid reactions.

The five days hunger period of Mr. J. H. L. began July 14 and was concluded July 19. During July 10 to 14 daily observations were made of the gastric hunger contractions, in order to establish the normal frequency and general character of these contractions in Mr. L. The periods of hunger contractions of Mr. L. under normal conditions of eating differ from those of the writer by usually ending in the incomplete tetanus previously described in Mr. V. This is probably due to the fact that Mr. L. is sixteen years younger than the writer.

Summary of the Observations on Mr. J. H. L.

Control Period

July 10. — No breakfast or lunch; 1:30–4:25 P.M. period of observation; 2:00–2:40 P.M. gradually increasing contractions ending in 11 strong contractions and strong tetanus ($3\frac{1}{2}$ min.). Feeble rapid contractions begin to reappear at 3:15 and gradually increase in amplitude.

July 11. — No breakfast; 9–12 A.M. continuous fairly strong contractions. Period of 15 strong contractions; 10:30–11:00 A.M.-11:00–12:00 continuous fairly strong contractions (22 contractions).

July 12. — No breakfast; 9:35–10:10 A.M. 22 contractions of gradually increasing strength in 30 minutes, ending in 3 minute incomplete tetanus.

July 13. — No lunch; 12:00–12:30 P.M. continuous fairly strong contractions. A small group (10) of strong contractions 12:30–

12:45. A period of strong contractions (22 gradually increasing ending in 3 minute tetanus) 1:50–2:30 P.M.

July 14. — 10 A.M.–1 P.M. No breakfast; 10:00–10:50, 31 gradually increasing strong contractions ending in tetanus (2 min.); 11:30–12:00 14 fairly strong contractions, no tetanus; 12:30–1:00, 21 gradually increasing strong contractions ending in a 3 minute tetanus.

Fasting Period. Last Meal July 14, 2 P.M. Body Weight 62.8 K.

July 15, P.M. — 7:45–8:25, 19 fairly strong contractions.
8:25–8:35, quiescence.
8:35–9:00, 28 fairly strong contractions.
9:00–9:15, quiescence.
9:15–9:45, period of 21 fairly strong contractions.
9:45–9:55, quiescence.
9:55–10:25, period of 21 fairly strong contractions.
10:25–11:00, period of 18 fairly strong contractions.
11:05–11:40, period of 17 fairly strong contractions.

Interruption

July 16, A.M. — 9:20–10:25, period of gradually increasing very strong contractions (33) ending in tetanus (2 min.).

Interruption

P.M. — 1:00–1:40, period of gradually increasing strong contractions (25) ending in tetanus (3 min.).

Interruption

3:55–5:00 quiescence.
5:00–5:50, period of fairly strong contractions (17). No tetanus.
8:35–9:35, period of very strong contractions (37) ending in 3 minute tetanus.
9:35–10:20, quiescence.
10:20–11:20, continuous fairly strong contractions.
11:20–11:30, fairly quiescent.
11:30–12:00, period of fairly strong contractions (11). No tetanus.

July 17, A.M. — 12:00–12:40, continuous feeble contractions.
12:40–1:30, quiescence.
1:30–2:00, continuous feeble contractions.
2:00–3:00, quiescence.
3:00–5:30, continuous feeble to fairly strong contractions.

Interruption

9: 30–10: 10, period of very strong gradually increasing contractions (36) ending in tetanus of $2\frac{1}{2}$ min.

Interruption

P.M. — 12: 15–3: 30, practically continuous feeble to moderately strong and strong contractions.

Interruption

8: 40–10: 00, continuous feeble to moderately strong contractions.

10: 00–10: 40, period of very strong gradually increasing contractions (20) ending in tetanus (2 min.).

10: 40–11: 00, quiescence.

11: 00–11: 50, period of moderately strong contractions (23). No tetanus.

July 18, A.M. — 11: 50–2: 30, mainly quiescent (occasional feeble contractions).

2: 30–3: 30, period of very strong gradually increasing contractions (34). No tetanus.

3: 30–4: 00, fairly quiescent (occasional feeble contractions).

4: 00–5: 00, period of strong gradually increasing contractions (24) ending in tetanus ($2\frac{1}{2}$ min.).

5: 00–5: 45, continuous feeble contractions.

Interruption

9: 20–10: 10, period of fairly strong contractions (35); no tetanus.

10: 10–11: 15, fairly quiescent.

11: 15–12: 00, period of strong contractions (22). No tetanus.

Interruption

P.M. — 2: 30–3: 50, continuous very feeble contractions.

3: 50–4: 05, period of 10 fairly strong contractions.

4: 05–4: 15, quiescence.

4: 15–4: 40, period of 13 strong contractions.

4: 40–4: 50, quiescence.

4: 50–5: 30, period of very strong contractions (22) ending in tetanus.

Interruption

8: 35–9: 20, 32 strong contractions practically continuous. Strong tonus.

9: 20–10: 00, continuous feeble contractions.
10: 00–10: 50, 15 strong contractions (long drawn out). One tetanus period.
10: 50–11: 30, period of strong contractions (22) ending in very strong tetanus (3 min.).
11: 30–12: 40, fairly quiescent, but a few fairly strong contractions.
July 19, A.M. — 12: 40–1: 25, period of very strong contractions (37). No tetanus.
1: 25–1: 45, quiescence.
1: 45–2: 15, period of fairly strong contractions (11.) No tetanus.
2: 15–2: 30, quiescence.
2: 30–3: 10, period of very strong contractions (22) ending in a 3 minute tetanus.
3: 10–4: 00, continuous very feeble contractions.
4: 15–6: 00, continuous strong contractions (36) ending in tetanus (3 min.). (Long and irregular pauses evidently due to psychic inhibition, as Mr. L. was very restless.)
End of experiment. Body weight, 59 K. Loss of body weight, 3.8 K.

It is clear that the results on Mr. L. practically duplicate those on the writer. (1) There is no decrease, but on the contrary, an increase in the gastric tonus and in the hunger contractions. (2) The hunger periods are apparently more frequent and intense at night during sleep than during the day. (3) The stomach showed an acid reaction all the time during the hunger period, evidently due to a continuous but scanty secretion of gastric juice.

2. *The Subjective Phenomena*

(A) *General condition.* — Mr. L. as well as the writer continued in good health and in fairly good spirit throughout the starvation period. On the fourth and the fifth day both men felt somewhat weak. Some mental depression was also experienced, especially on the fifth day by Mr. L., who complained of feeling dizzy on getting on his feet after lying down. An

hour's lecturing seemed quite an effort on the fourth starvation day, and on the fifth day both men felt distinctly better when lying down than when sitting or standing. Both men slept fairly well during the four nights of the starvation period, despite the persistent hunger contractions and the unusual surroundings of the research laboratory as a sleeping room. Defecation did not take place after the first day. The secretion of urine was diminished although water was taken whenever desired. In some cases a glass of water was taken to diminish the hunger pangs. The writer did not enjoy the cigar after the second day; in fact, smoking tended to produce nausea.

(B) *The Sensations of Hunger and Appetite.* — During the period of control observations both subjects trained themselves

FIGURE 2. (About one-third the original size.) Record of the end of a typical period of gastric hunger contractions of J. H. L. (age 22) after five days starvation. Mr. L. was asleep lying on the right side. At *X* he turned over on the back without waking up. During the strongest hunger contractions Mr. L. moaned but did not wake up. Showing persistence of powerful hunger contractions of the empty stomach during prolonged starvation.

in judging the relative intensity of the individual hunger pangs, and in this both of them attained a fair degree of efficiency. They can invariably tell the onset of a hunger period before the contractions have reached a sufficient intensity to be recognized as individual hunger pangs. This initiation of the hunger period consists in a gradually increasing tonus and feeble and more or less rhythmical contractions, and this is felt as a continuous mild hunger or a moderate degree of steady and somewhat uncomfortable tension in the epigastric region. This sensation is

not dependent on or influenced by the distended rubber balloon in the stomach cavity. In this way one can usually manage to record practically every hunger period during the day, simply by starting observations as soon as one feels the very onset of the hunger period. The periods of *strongest* hunger contractions, or the hunger tetanus, are also felt as continuous and intense hunger. And there is a characteristic sensation of relief or diminished tension within a minute or so after the period of hunger contractions is at an end.

During the first two or three days the hunger sensation seemed both to Mr. L. and the writer somewhat more severe than any hunger experienced during the control period, in fact, more severe than seemed warranted from the degree or intensity of the gastric contractions. To be sure, the *hunger contractions* of the stomach were usually somewhat stronger and in every case at least as strong as during the control period, but the *hunger sensation* seemed even stronger proportionately. During the fourth and the fifth hunger days, on the other hand, the hunger sensation seemed somewhat weaker than one could have predicted from the intensity of the hunger contractions. In fact the sensation did not even seem to be as keen as that produced by a period of strong hunger contractions 6 to 10 hours after the previous meal. The reader will recall that the gastric hunger contractions on the last two days of starvation were of normal or greater than normal intensity.

The sensation of hunger was almost continuous after the first day of starvation. That is to say, the hunger sensation referred to the epigastrium did not wholly disappear during the intervals between the periods of vigorous gastric contractions. This feeble but continuous hunger sensation is evidently caused by the increased gastric tonus and more or less continuous but feeble rhythmical contractions that represent the periods of relative quiescence of the empty stomach during prolonged starvation (Fig. 3). On the fifth day of starvation the continuous hunger sensation seemed to be tinged with a peculiar "burning" sensation, also referred to the stomach, the fusion resembling somewhat the feeling of "sick stomach," with its attendant central depression. This "burning" sensation was

probably caused by acid stimulation of hyperexcitable nerve endings in the gastric mucosa.

The appetite during the starvation period ran practically parallel with the sensation of hunger. It was distinctly increased the first two or three days, and diminished on the fourth and fifth days. In fact, the depression of appetite on these two days seemed distinctly greater than the depression of the hunger sensation. Instead of an eagerness for food, there was almost an indifference towards food, despite the persistent hunger call of the empty stomach. This was particularly true of Mr. L. He stated several times on the fourth and fifth day that the

FIGURE 3. (Four-fifths the original size.) Record from the empty stomach of A. J. C. on the fourth day of starvation, showing the 20-seconds rhythm of varying intensities that usually persist between the periods of strong hunger contractions in prolonged starvation. When this type of activity was present the writer experienced a *continuous hunger*, but less intense and uncomfortable than the hunger pangs from the strong contractions. The writer was unable to distinguish in consciousness the individual hunger pangs of this rapid and feeble gastric activity. The sensation seemed continuous.

sight of food led, not to a feeling of eagerness for eating, but to a feeling partaking of the nature of revulsion or nausea. This was not experienced by the writer. Food looked good to him throughout the starvation period, but he found it much easier to dismiss thoughts of food and eating from his mind towards the end than at the beginning of the period.

The reasons for the above seeming discrepancy in the parallel between the intensity of gastric hunger contractions and the intensity of the subjective hunger sensation during the five days hunger period can only be conjectured at present. We are inclined to believe that the weakening of the hunger and the appetite sensations towards the end of the period is due to a

depression of the central nervous system. This central depression, however caused, was clearly in evidence both in Mr. L. and in the writer. Afferent impulses from the viscera differing from the normal quantitatively or qualitatively probably also play a rôle.

(C) *The After Effects of the Starvation Period.* — Both in Mr. L. and the writer *practically all of the mental depression and some of the feeling of weakness disappeared during the partaking of the first meal after the fasting period.* This central depression is therefore essentially a reflex condition depending probably on afferent impulses from the digestive tract, rather than a result of lack of nutrient material in the blood. But complete recovery from the bodily weakness did not take place till the second or third day after breaking the fast.

From the second day on both men felt unusually well, distinctly better, in fact, than before the hunger period, although both men are normally in good health and vigor and not hampered by excessive fat. The writer felt as if he had had a month's vacation in the mountains. The mind was unusually clear and greater amount of mental and physical work was accomplished without fatigue. In the writer's own case the five days starvation period increased the vigor of the gastric hunger contractions to that of a young man of 20 or 25, and the empty stomach retained this increased vigor for at least three weeks after the hunger period, when observations were discontinued owing to absence from the University. This improvement, or rejuvenation of the stomach, is not a matter of subjective feeling or opinion, but a matter of objective record on the tracings. Neither Mr. L. or the writer can be considered as ordinarily eating to excess, although the daily intake of protein and total calories are greater than the minimum requirement advocated by Chittenden. The cause of the improvement was not loss of excessive adipose tissue.

Mr. L. states that the augmentation of hunger and appetite persisted at least for two or three weeks after the end of the starvation period.

The writer has long been familiar with but not particularly impressed by the enthusiasts who advocate starvation as a

panacea for various ills. But this personal experience leads him to suspect that there is more value in some of these measures than is ordinarily considered. Civilized man has travelled far from the conditions of life among wild animals and primitive man, with whom periods of enforced starvation are not uncommon. Occasional periods of starvation, say once or twice a year, in the case of healthy adult persons, may not only add to the joy of living but also to the length of life.

(D) *The Discomforts of Starvation.* — During the entire starvation period the hunger sensation was strong enough to cause some discomfort, but not to a degree that could be called marked pain or suffering. The discomfort was at no time sufficient to interfere seriously with work. And since practically all observers agree that the hunger discomfort is greatest during the first few days of starvation it seems probable that our five days starvation period gave us a taste of the maximum discomfort that would be experienced in more protracted fasts. Accounts of acute sufferings from mere starvation (water being at all times available) must therefore be wholly imaginary, or the result of fear and panic. Voluntary starvation is in no sense an heroic act, and citation of hunger experiments on animals in the interest of science as instances of cruelty to animals is without foundation.

III. Results on Dogs

1. *Normal Dogs*

No attempt was made to take continuous records of the motor activity of the empty stomach in the starving dogs. Observations were made for periods of 2 to 6 hours each day, beginning the second or third day of starvation. The result on the four normal dogs can be seen at a glance from the following summary:

Dog I. — *Young Vigorous Female*

Starvation Day:

2d day — 10: 25–12: 00 A.M., continuous vigorous contractions, type II and III.

3d day — 2:00–4:00 P.M., continuous vigorous contractions, type II mainly.

4th day — 10:25 A.M.–12:35 P.M., continuous contractions, type II mainly.

5th day — 1:30–3:30 P.M., continuous contractions, type II mainly.

6th day — 10:55 A.M.–1:00 P.M., continuous contractions, type III mainly.

7th day — 9:00–12:00 A.M., continuous contractions, type III mainly.

8th day — 9:35–11:35 A.M., continuous contractions, type II mainly.

9th day — 10:35 A.M.–12:35 P.M., continuous contractions, type III mainly.

10th day — 9:35 A.M.–3:35 P.M., very vigorous contractions, type II and III only. Tonus on the average, 12 cm. bromoform.

End of Experiment.

Dog II. — *Young Vigorous Female*

3d day — 10 A.M.–3 P.M., strong tonus and continuous contractions of type III.

4th day — 10–12 A.M., strong tonus and continuous contractions of type III.

5th day — 1:00–3:00 P.M., strong tonus and continuous contractions.

6th day — 9–12 A.M., strong and continuous contractions. Tonus about 10 cm. bromoform.

End of Experiment.

Dog III. — *Old Female*

2d day — 10–12 A.M., feeble contractions, type I.

3d day — 9–11 A.M., a few irregular contractions, type I; stomach hypotonic.

4th day — 1–3 P.M., a few irregular contractions, type I; stomach hypotonic.

5th day — 8–11 A.M., practically no contractions; stomach hypotonic.

6th day — 1–4 P.M., practically no contractions; stomach hypotonic.

End of Experiment.

Dog IV. — *Young Vigorous Female*

3d day — 9:30–11:30 A.M., strong tonus, continuous contractions, types II and III.
4th day — 1–3 P.M., fairly strong tonus, type I and II contractions.
5th day — 8–11 A.M., strong tonus, type II and III contractions.
7th day — 9:40–12 A.M., fairly strong tonus, type III contractions.
8th day — 1–3 P.M., very strong tonus, type III contractions.
9th day — 8–10 A.M., feeble tonus, feeble contractions, type II.
10th day — 8–11 A.M., fairly strong tonus; fairly strong type II contractions.

End of Experiment.

Dogs I, II and IV exhibited *either normal or greater than normal hunger contractions of the empty stomach during the entire starvation period.* The increased tonus of the stomach was particularly marked. In consequence of this increased tonus the types of hunger contractions were usually those previously described as II and III, that is practically incomplete tetanus. Judging from observations on man the dogs probably felt continuous and intense hunger during these contractions. Typical records from Dog I on the eighth and tenth days of starvation are reproduced in Fig. 4.

The only old dog in this series, No. III, had shown rather feeble and irregular gastric hunger contractions before the starvation period. The reason for this was not apparent. The dog was in good condition and would eat greedily, even when the empty stomach was practically quiescent and distinctly hypotonic. This dog showed virtually no gastric hunger contractions after the third day of starvation, and the stomach appeared distinctly hypotonic. The dog was eager for food, however.

The stomachs of all four dogs showed acid reaction throughout the hunger period, just as was the case with the stomachs of the starving men.

It will thus be seen that the empty stomach of men and dogs exhibits ordinarily either normal or greater than normal hunger contractions during starvation periods of from 5 to 10 days.

The cause of this increased hunger activity of the stomach may be —

1. An increase in the tonus innervation via the vagi.
2. Changes in the blood in consequence of starvation.
3. The starvation metabolism of the motor tissues of the stomach itself.

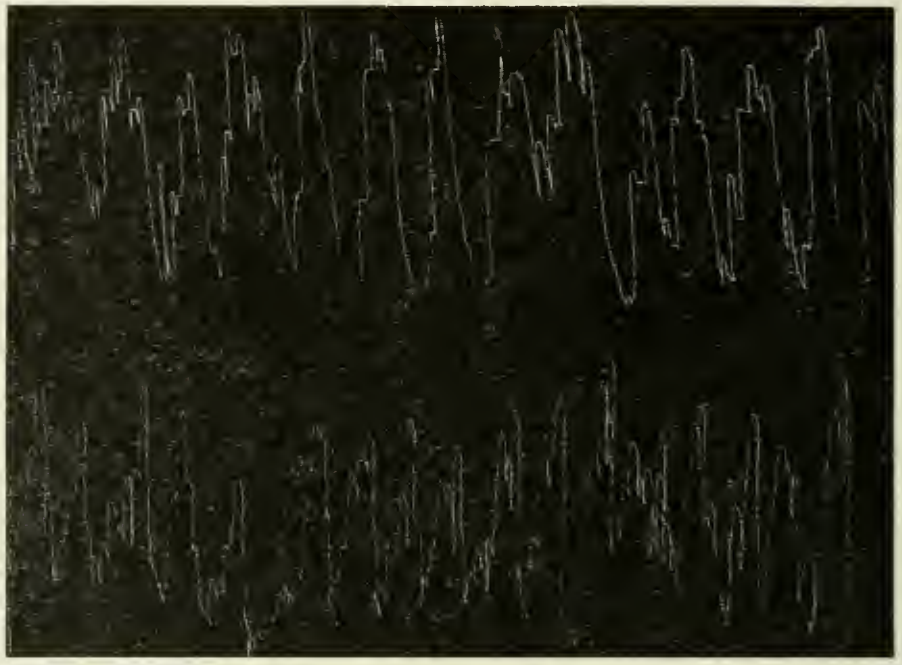


FIGURE 4. (About one-half the original size.) Typical record (10 minutes) of the hunger contractions of the stomach of Dog I. *A*, after eight days starvation; *B*, after ten days starvation. Showing a persistence of the gastric hunger contractions during prolonged starvation.

2. *Dogs with the Stomach Isolated from the Central Nervous System*

In order to decide between these three possibilities starvation tests were made on two dogs with complete isolation of the stomach from the central nervous system by section of the vagi and the splanchnic nerves and on one dog with the vagi nerves severed, the splanchnic nerve being left intact. The following is a brief summary of the results:

DOG V. — *Young Female. Section of the Vagi and Splanchnic Nerves Two Weeks before Starvation Period*

Starvation Day:

4th day — 10 A.M.–1 P.M., one group, type I contractions (15), fairly strong.

5th day — 2–5 P.M., type I contractions, fairly strong but with long intervening pauses.

6th day — 10–12 A.M., 30 strong (type I) contractions ending in tetanus (Fig. 5A).

7th day — 1–4:30 P.M., continuous contractions of type III; tonus about 10 cm. bromoform.

End of Experiment

Dog VI. — *Adult Fairly Vigorous Female. Vagi and Splanchnic Nerves Cut*

5th day — 9–11 A.M., 9 very vigorous contractions and tetanus periods (in 20 min. contractions).

6th day — 1–3 P.M., fairly strong contractions of type I; long pauses between contractions.

7th day — 1–5 P.M., stomach hypotonic; no contractions.

End of Experiment

Dog VII. — *Young, Fairly Vigorous Female. Vagi Nerves Sectioned*

3d day — 9–11 A.M., fairly strong type I contractions.

5th day — 1–5 P.M., strong (type I) contractions (27); long pauses between.

6th day — 9–11 A.M., stomach hypotonic, practically no contractions.

7th day — 1–4 P.M., fairly strong type I contractions, prolonged and partly tetanic; long pauses between contractions (Fig. 5B).

End of Experiment

The gastric hunger contractions of Dog IV were absent on the seventh day of starvation, but Dogs V and VII showed either normal or greater than normal hunger contractions throughout the starvation period. Since the increase in the hunger contractions appeared to be just as marked in the dogs with the stomach isolated from the central nervous system as in normal dogs, it follows that the cause of this increase is not an augmentation of the vagus tonus. I propose to determine whether the increase is due to changes in the blood or to the starvation metabolism of the stomach tissue itself by transfusion experiments.

These starvation periods were not of sufficient length to cause very marked asthenia either in the men or in the dogs. The present data do not, therefore, answer the question to what

extent the motor mechanism of the empty stomach shares in the general asthenia produced by more protracted fasting. They do show that the hunger contractions persist with normal or greater than normal vigor during shorter starvation periods. These positive results show, further, that the exceptional cases

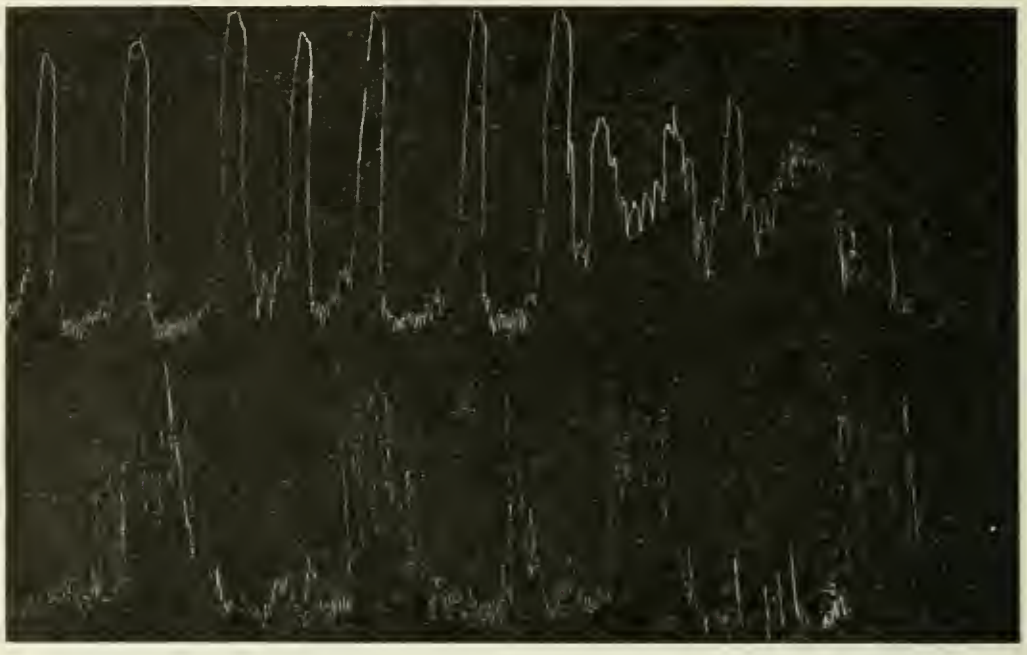


FIGURE 5. (Four-ninths the original size.) *A*, tracing showing end of hunger period of Dog V after six days of starvation. The vagi and splanchnic nerves sectioned before the starvation period. *B*, typical hunger contractions of Dog VII after seven days starvation. Section of both vagi before the starvation period. Showing persistence and increase of hunger contractions of the stomach isolated from the central nervous system in prolonged starvation.

of gastric hypotonus and decreased gastric motility are not due to starvation as such, but to special and exceptional factors. The depression may be due (1) to a primary asthenia of the stomach; (2) central inhibition via the splanchnic nerves (pains, depression, etc.); (3) acid inhibition from the stomach mucosa owing to copious secretion of gastric juice. This question requires further investigation.

IV. Discussion of the Results

So far as we are aware, this is the first time that actual records have been taken of the gastric hunger contractions in man during prolonged starvation; and also the first time that

the physiologists themselves have done the starving. But we have many accounts of the subjective feeling of hunger and appetite in man during long fasts. A comparison of these accounts with our own results is rendered difficult by the confusion of the sensations of hunger and appetite that unfortunately obtains in physiological and medical literature. Leaving out the cases complicated by water starvation, there appears to be a general agreement that the sensations of hunger and appetite increase during the first few (2 to 3) days of starvation, and then decrease even to complete abolition. Succi reverted to drugs to deaden the hunger pangs only during the first two days of his 30-day fast.[1] Viterbi, who starved himself to death voluntarily, noted complete absence of hunger after the fifth day.[2] Cetti and Breithaupt.[3] did not experience any discomfort from hunger after the first few days, but it is not clear that hunger and appetite was altogether lacking. The young man starving for five days under the observation of Johansson, Landergren, Sondén and Tigerstedt[4] complained of weakness, dizziness and cold, but did not feel particularly hungry at the end of the fast. Carrington[5] cites many cases of men and women in prolonged starvation where hunger sensation subsided or disappeared after the third day. All these persons cited by the last author were, however, suffering from this, that or the other ailment, and some of them were lying in bed during the entire starvation period. These remarks apply also to various recent popular accounts of cases of prolonged fasting to cure digestive or nervous disorders. All cases of compulsory starvation (persons shipwrecked, explorers, and hunters lost or cut off from supplies, etc.) are usually complicated by lack of water, by the effects of explosure, and by fear, panic, etc., so that the state of the actual hunger sensation cannot be determined.

[1] Luciani: Das Hungern, Leipzig, 1890.

[2] Quoted by Luciani, Physiologie des Menschen, 1911, iv, p. 65.

[3] Lehmann, Muller, etc.: Archiv für pathologische Anatomie, Supplement B, 1893, p. 131.

[4] Johansson, etc.: Skandinavisches Archiv für physiologie, 1896, vii, p. 33.

[5] Carrington: Vitality, Fasting and Nutrition, New York, 1908.

All these accounts are based on the statements of persons who were in no sense trained observers. In view of that fact I think the consensus of opinion that hunger disappears after the third day of starvation means no more than that after the third day the hunger sensation is not so persistent or painful as to dominate consciousness.

There was, certainly, some decrease in the hunger and especially in the appetite sensation of the writer, and of Mr. L. on the fourth and the fifth days. But it was a decrease of, not an absence of hunger sensation. It has already been pointed out that the decrease in intensity of the hunger sensation was not due to a decrease in the intensity of the gastric hunger contractions, but to depression of the central nervous system, or some disturbance in the complex of impulses from the intero- and proprioceptors. I do not deny the possibility that the sensation of hunger may actually disappear in some persons after two or three days fasting, but this is not due to starvation as such, but to special conditions, such as primary asthenia of the stomach, great cerebral depression, inhibition via the splanchnic nerves through pain or other factors causing hyperactivity of the sympathetic system, or to copious and continuous secretion of gastric juice causing acid inhibition. In view of our results on dogs, it seems probable that during periods of prolonged starvation the sensation of hunger will prove most persistent in young and vigorous persons.

Our work on dogs is a repetition and extension of the work of Boldireff.[1] This observer states that the periodic contractions of the empty stomach in dogs become feeble and irregular during prolonged fasting and cease entirely after a fast of 3 to 4 days. After that time there is a copious and continuous secretion of gastric juice. If this spontaneous secretion of gastric juice is sufficiently rapid, there will, of course, be an acid inhibition of the hunger contractions.

Only one of our dogs (No. III) corroborates the results of Boldireff. Dog III showed practically no hunger contractions after the third day. The reader will recall that this was the

[1] Boldireff: Archives des sciences biologiques, 1905, xi, p. 1.

oldest dog in the series, and that he had shown relatively weak and irregular hunger contractions during the control period before starvation. This fact probably indicates an asthenic condition of the stomach, in addition to the certain factor of age.

The reader will recall that Boldireff's dogs had duodenal, biliary, and pancreatic fistulæ, in addition to the fistula of the stomach. As these dogs were thus subjected to greater disturbance of digestion and metabolism than were the dogs used in our starvation tests, it seems probable that the dogs used by Boldireff were subnormal in the way of some asthenia of the digestive tract. This may be a factor in the early disappearance of gastric contraction during the prolonged starvation. Multiplication of fistulæ also increases the chances for reflex inhibition of the stomach from adhesions, pain, etc. While the difference in Boldireff's results and our own may be due mainly to the difference in the condition of the dogs at the beginning of the hunger tests, it may also be noted that Boldireff's method of registering the gastric contractions was not delicate enough to show the weaker contractions and the variations in tonus. The strong continuous tonus and rapid contractions ("Type III") which I have designated the "hunger tetanus" would probably not have been recorded on Boldireff's tracings. It was precisely this hunger tetanus which was mostly in evidence in our normal starving dogs (see records of Dogs I, II, and IV, and Fig. 4).

Boldireff found that during the first three days of starvation there are periods of apparently spontaneous secretion of gastric juice, and during this secretion the gastric contractions ceased. After the third day the gastric secretion became continuous. We did not subject our dogs to the additional inconvenience of accurate determination of the rate of gastric secretion, but incidental observations in other lines of work on cats with the stomach pouch of Pawlow have convinced me that there may be considerable fluctuation in the rate of the secretion of the empty stomach. The secretion of gastric juice must be relatively rapid, however, in order to maintain complete inhibition of the tonus and contractions of the healthy and vigorous stom-

ach through acid stimulation of local and long reflexes. The stomach of the writer, of Mr. L. and of all the dogs was acid throughout the starvation period, which indicates a more or less continuous secretion of gastric juice, even during the first three days of starvation. But the quantity or strength of hydrochloric acid in the stomach at any one time was not sufficient to produce the acid inhibition either in man or dog.

That starvation will ultimately lead to marked weakening (and eventually absence) of the sensation of hunger owing to depression of the central nervous system and asthenia of the gastric motor mechanism is self evident, but in young and vigorous animals this depression is practically absent until the skeletal neuro-muscular asthenia is very marked. That prolonged starvation, in the case of healthy individuals, should completely abolish the sensation of hunger and appetite while the organism is still in fair state of integrity is inherently improbable. When it does occur, it is probably due to pathological complications. Starvation increases the desire for food (that is hunger and appetite) in wild animals, at least up to the point where the asthenia reaches a degree that renders locomotion impossible. This is shown by the increased boldness and disregard of danger on the part of the starving animal (herbivorous as well as carnivorous) in his search for food. Certain wild animals (particularly reptiles) when in captivity are apparently an exception, for it is known that some of these animals will voluntarily starve to death, unless fed forcibly. The mechanism of this striking inhibition of the normally all powerful hunger sensation is not known. The gastric hunger contractions during prolonged starvation probably present special conditions also in hibernating animals during the hibernation. Possibly the depression of the central nervous system (even in species not actually "asleep") is sufficient to prevent the impulses initiated by the contracting stomach from reaching consciousness.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

IX. The Hunger Contractions of the Stomach Pouch Isolated according to the Method of Pawlow

By A. J. CARLSON, J. S. ORR, and L. W. McGRATH

[*From the Hull Physiological Laboratory of the University of Chicago*]

THIS work was undertaken in order to determine whether the rapid contractions of the empty stomach (continuous contraction of 20 seconds duration in man, 12 to 15 seconds duration in dogs) as recorded by means of an inflated balloon in the cavity of the stomach represent contractions of the fundus musculature or are pressure variations from contractions of the antrum pylori. This second alternative is suggested by the fact that the rate of this rhythm of the empty stomach is identical with the rate of the digestion peristalsis of the antrum pylori in man and dog.

It was also hoped that simultaneous records of the contractions of the stomach pouch and of the main stomach would throw some light on the relative importance of the tonus of the vagi, the condition of the blood, and the physiological state of the gastric motor mechanisms in the genesis of the hunger contractions. The Pawlow operation leaves the vagi connections with the stomach pouch at least partially intact, so that if the hunger contractions are normally initiated by efferent vagi impulses we might expect a close parallel between the rate and intensity of the contractions in the two stomachs. The character of the blood flowing to the two stomachs is necessarily the same. The amount of local nervous coördination between the two stomachs depends on the extent of the intact myenteric plexus and muscularis. The operation severs by far the greater amount of these neuro-muscular connections. This may dimin-

ish the local nervous coördination and thus permit the development of different physiological states of the motor mechanisms in the two stomachs. The work was done on two young and vigorous dogs. Relatively large stomach pouches were made according to the method of Pawlow. In Dog I the muscularis joining the two stomachs was left intact for a distance of six centimetres. In Dog II the muscular union was reduced to three centimetres. These figures were verified by post-mortem examination at the end of the experiment.

Simultaneous records of the hunger contractions in the two stomachs were taken while the dogs were lying quietly and comfortably in the lap of an attendant. The balloon was passed into the main stomach via the oesophagus. The balloon used for the stomach pouch was much smaller than that used for the main stomach.

Results

Dog I, having the 6 cm. of intact muscularis and myenteric nerve plexus uniting the two stomachs, showed a fairly close

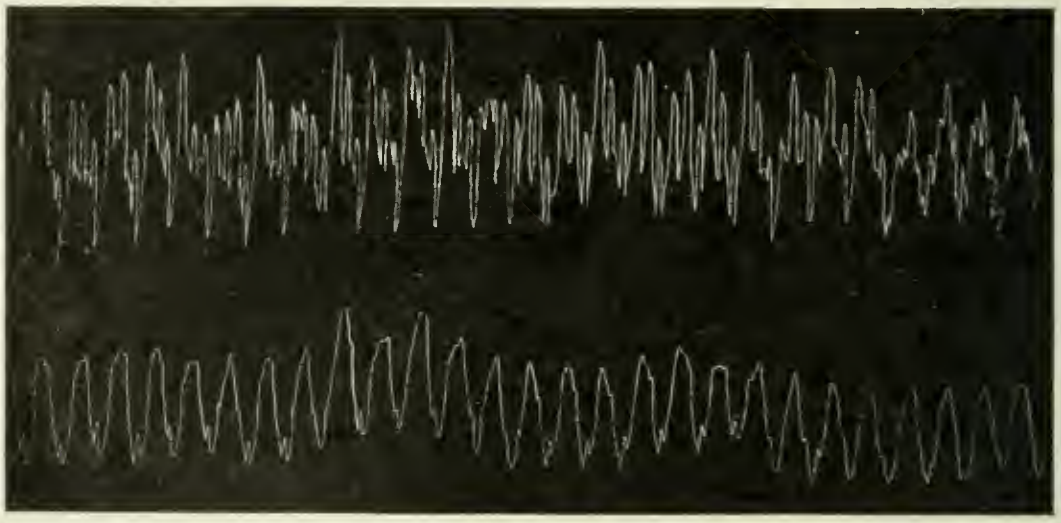


Figure 1. (Two thirds the original size.) Simultaneous records of the hunger contractions of the main stomach (upper curve) and the stomach pouch (lower curve) of Dog I. Both stomachs in strong tonus and Type III hunger contractions. Showing practically complete synchrony of the two stomachs.

parallel of the tonus and the hunger contractions of the main stomach and the stomach pouch. When the tonus of the stomach was so great that the Type III contractions (or

incomplete tetanus) were present the synchrony appeared complete. The two stomachs gave contractions of the same strength and rapidity. The contraction and relaxation phases of the individual contractions show also a fair degree of correspondence. A typical tracing showing this synchrony in Dog I is reproduced in Fig. 1.

When the gastric tonus is weaker so that the stomach exhibits the slower and stronger contractions of Type II, the parallel between the stomachs is still in evidence, but it is less complete. That is to say, the contractions may appear simultaneously and be of corresponding strength, they may appear simul-

FIGURE 2. (Two fifths the original size.) Simultaneous record of the hunger contractions of the main stomach (upper curve) and the stomach pouch (lower curve) of Dog I. Type I contractions and fairly close coördination of the two stomachs.

taneously and be very unequal in strength, or there may be considerable lack of synchrony both in the beginning and in the duration of the contractions of the two stomachs. At times the pouch would give two separate and strong contractions during a single but more protracted contraction of the main stomach. When the contractions are still slower, or of Type I, the coördination between the two stomachs is more nearly perfect, as shown by the typical records reproduced in Fig. 2.

Dog II, with only 3 cm. intact muscularis and myenteric plexus uniting the two stomachs, exhibited no synchrony between the two stomachs at any time. The main stomach would be

quiescent, while the pouch showed vigorous hunger contractons, or vice versa. But more frequently both stomachs exhibited

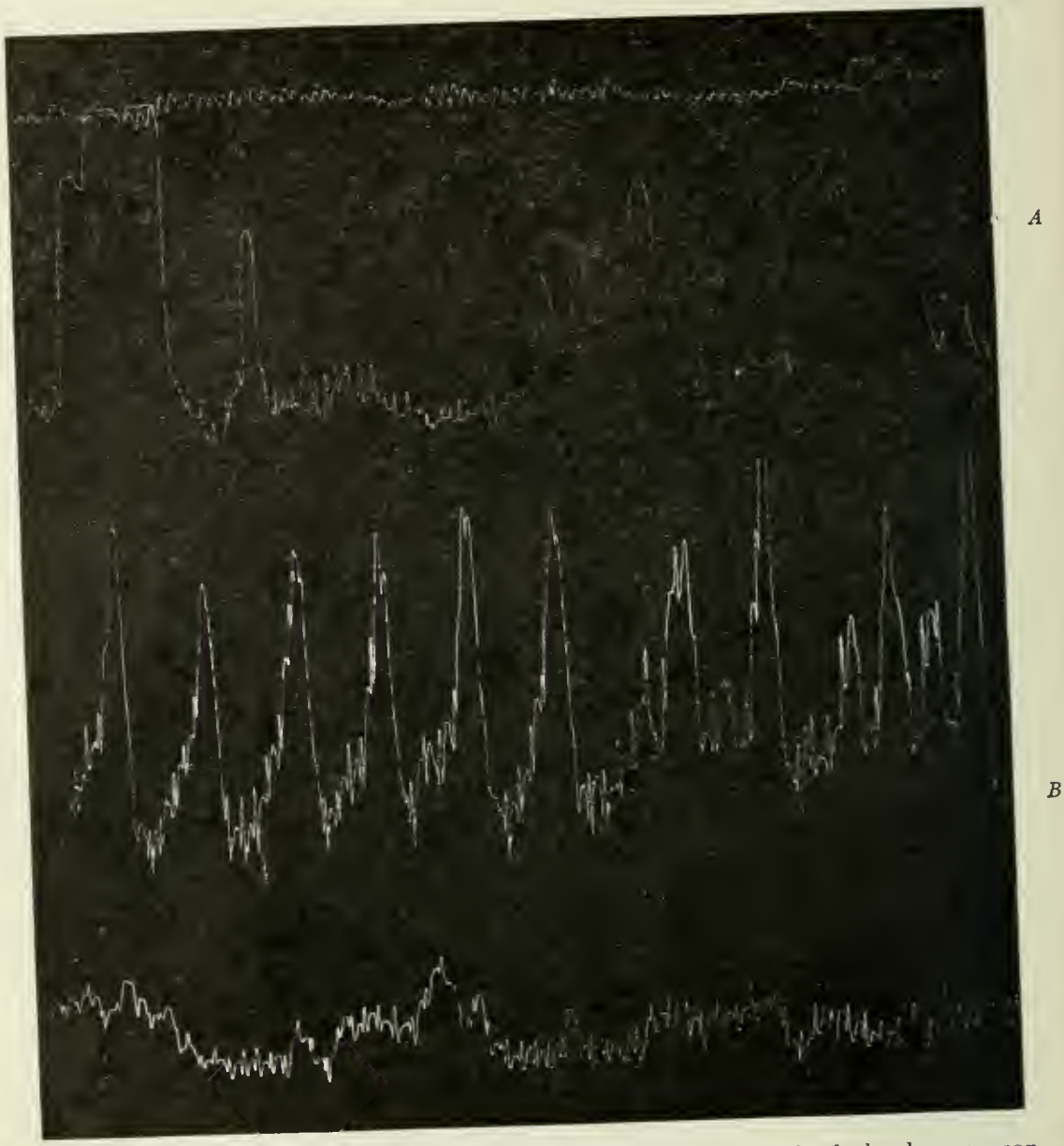


FIGURE 3. (Two thirds the original size.) Simultaneous record of the hunger contractions of Dog II. *A*, strong contractions of pouch (lower curve) during quiescence of main stomach (upper curve). *B*, strong contractions of main stomach (upper curve) during quiescence of pouch (lower curve). Showing that the initiation of the period of hunger contractions is not primarily due to the character of the blood.

hunger rhythm at the same time, but without any synchrony in the rate and the strength of the contractions. Tracings illustrating these phenomena in Dog II are reproduced in Figs. 3 and 4.

The Pawlow operation necessarily severs a considerable portion of the vagi connection with the pouch. But it is well known that at least half of the vagus influence can be eliminated by section of one vagus without any appreciable disturbance of the gastric tonus. In general the hunger rhythm of the pouch in Dog II resembled that of the stomach in dogs with section of both vagi. In this animal (Dog II) the amount of vagi connections with the motor mechanism of the pouch was not sufficient to maintain the normal tonus. It is also evident

A *B*

FIGURE 4. (One third the original size.) Simultaneous record of the hunger contractions of the main stomach (upper curve) and the stomach pouch (lower curve) of Dog II. *A*, feeble tonus and slow contraction of puch during strong tonus and rapid contraction of main stomach. *B*, stronger tonus and more rapid contractions of the pouch than of the main stomach.

that the 3 cm. bridge of myenteric plexus was also insufficient for local coördination of the two stomachs. In Dog II, therefore, the two stomachs differed in the quantity of vagi innervation. The other obvious differences between the main stomach and the pouch, such as the presence of saliva, the occasional presence of intestinal juice and bile, gases, and food debris, hair, etc., were common for Dogs I and II. These conditions were not sufficient to create incöordination through differences in the physiological state of the motor mechanisms when the connecting bridge of myenteric plexus was 6 cm.

The fact that in Dog II the pouch would show the hunger contractions during complete quiescence of the main stomach

and vice versa seems to show that the physiological state of the gastric motor mechanism and not the character of the blood is the primary factor in the genesis of these contractions. The main stomach and the pouch were supplied with the same blood. The character of the coördination of the two stomachs in Dog I indicates that the hunger contractions are not normally caused by periodic impulses from the brain via the vagi. If such were the case there should have been a closer synchrony of the contraction and relaxation phases in the main stomach and the pouch. A primary vagi innervation of the contractions would not permit a contraction in the pouch with no sign of contraction in the main stomach, the beginning of the pouch contraction during the relaxation phase of the main stomach, or two distinct and strong contractions of the pouch during a single contraction of the main stomach. These results are readily explainable on the basis of local genesis of the contractions and some impairment of the myenteric connections between the two parts. Under these conditions the physiological state of the motor mechanism of the two stomachs would not be exactly alike, and in consequence there will be some interference with, or inhibition of the excitation wave at the isthmus joining the two parts, as well as in the two stomachs themselves. Thus the excitation wave from the main stomach may pass the myenteric bridge unimpeded, but reach the pouch during the refractory phase of the latter, and thus produce little or no effect. And a similar interference may obtain in the case of the excitation waves from the stomach pouch. Since most of the myenteric plexus joining the two parts of the stomach is severed in the Pawlow operation, the local coördinating mechanism is obviously impaired, although not completely destroyed. And if we assume a peripheral origin of the hunger contractions, this must lead to a certain degree of independent activity of stomach and pouch. The results demanded by this assumption of a peripheral stimulus or local automatism initiating the hunger contractions are those actually found in Dog I, that is, impaired synchrony of the two parts. As we have seen, the synchrony of the two stomachs is more nearly perfect the slower the contractions. When the contractions come at longer

intervals there is less chance for interference with the excitation wave in the region of the myenteric isthmus, and collision, so to speak, with the refractory state. The parallel in the activity of the two stomachs during Type III contractions may be apparent or a parallel of the tonus only; for when the tonus reaches a certain degree the contractions appear at their maximum rapidity. Hence if the main stomach and the pouch have equally strong tonus they will exhibit an equal number of contractions per unit of time even without any physiological coördination of the excitation waves between the two stomachs.

Conclusions

1. The fundus tissue of the empty stomach is capable of the rapid contractions that characterize the digestion movements of the pylorus part of the stomach; these rapid contractions of the fundus depend on a certain degree of tonus of the motor mechanism.

2. The character of the parallel between the hunger contractions of the main stomach and of the stomach pouch supports the view that these contractions are caused primarily by a gastric automatism and not by motor impulses via the vagi nerves.

3. When the muscularis and myenteric isthmus joining the main and the accessory stomachs is relatively narrow, the two stomachs exhibit complete independence of the hunger contractions even to the point of vigorous activity of the one during quiescence of the other. This fact points to a local automatism as the primary factor rather than the condition of the blood; as the character of the blood flowing to the main stomach and the stomach pouch is necessarily the same.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

X. The Condition of the Oesophagus during the Periods of Gastric Hunger Contractions

By A. J. CARLSON and A. B. LUCKHARDT

[*From the Hull Physiological Laboratory of the University of Chicago*]

A CLOSER study of the tonus of the oesophagus during the hunger contractions of the empty stomach might reveal the relation of the vagi to these contractions. There is some evidence in the literature of contractions of the oesophagus synchronous with the periods of gastric hunger contractions. Some people refer the hunger sensation or hunger pangs not only to the stomach, but also to the chest and throat.[1] This appears to be true not only of ignorant people, such as those interrogated by Schiff, but also of some people with special training in introspection.[2] Meltzer and Auer[3] have shown that stimulations of the central end of one vagus, the other vagus being intact, lead to a reflex contraction of the entire oesophagus. While it is probable that the main afferent path of this reflex is made up of the sensory nerves distributed to the oesophagus itself,[4] there is also a possibility that the reflex can be evoked by the afferent fibres in the vagi distributed to the walls of the stomach, and these fibres are stimulated by the gastric hunger contractions.[5] Cannon and

[1] Schiff: Physiologie de la digestion, Florence, 1867, p. 31.

[2] Our colleagues in the Department of Psychology, Professor J. R. Angell and Dr. Stella Vincent, inform us that in their cases the hunger sensation appears to be referred not only to the stomach, but also to the oesophagus and the throat.

[3] Meltzer and Auer: Zentralblatt für Physiologie, 1906 xx, p. 338.

[4] Meltzer: Proceedings of the Society for experimental biology and medicine, 1907, iv, p. 35.

[5] Carlson: This journal, 1913, xxxi, p. 308.

Washburne [1] have reported periodic contractions of the lower end of the oesophagus in man, and these contractions seemed to give rise to hunger pangs just as in the case of the contractions of the empty stomach. These authors suggest that the oesophagus contractions are synchronous with the gastric hunger contractions, but they did not prove the hypothesis by recording the stomach and oesophagus contractions simultaneously. The view that the gastric hunger contractions are accompanied by similar contractions of the oesophagus is also strengthened by the observations of Boldireff that contractions of the small intestines occur during the period of gastric hunger activity.[2]

If the gastric hunger contractions are synchronous with contractions of the oesophagus, the oesophageal contractions may be due to:

1. Extension, via local conduction paths in the myenteric plexus, of the excitation wave from the fundus to the oesophagus, especially the lower third composed mainly of non-striated muscle and provided with a myenteric plexus. If this is the case it is likely that the excitation wave does not spread to the region of the eosophagus composed of striated musculature and where the myenteric plexus is wanting. This possibility can be definitely proved or disproved by complete resection of the oesophagus just above the diaphragm, leaving the vagi intact, as this operation abolishes the oesophageal contractions, at least until regeneration of the myenteric plexus has been accomplished.

2. Motor impulses through the vagi synchronous with motor impulses to the stomach. If this is the case the gastric and the oesophageal contractions should correspond in rate and intensity. And there should be no hunger contractions in the lower oesophagus after section of the vagi in the chest, unless the oesophageal contractions can also be originated locally. We have seen that this operation does not abolish the gastric hunger contractions. If the oesophageal contractions synchronous with the periods persist after section of the vagi, they are probably due to extension of the excitation wave from the fundus and may actually lag behind the stomach contractions.

[1] Cannon and Washburne: This journal, 1912, xxix, p. 441.

[1] Boldireff: Archives des sciences biologiques, 1905, ix, p. 32.

3. A long reflex: afferent impulses from the stomach via the vagi to the medulla, stimulating the motor neurones to the oesophageal musculature. This possibility is suggested by the fact that the afferent impulses initiated by the gastric hunger contractions increase the tonus and reflex excitability of the whole cerebro-spinal axis. If this is the mechanism, the gastric contractions will precede the oesophageal contractions, and the latter are apt to show greater variability in amplitude. One would also expect the contractions to be in evidence even in the portion of the oesophagus composed of striated musculature and devoid of myenteric plexus.

It is clear from the above that an analysis of the relation of the gastric hunger contractions to the oesophageal tonus and contractions must throw more light on the relation of the vagi to the stomach contractions. The settlement of this question is important, for in our search for methods of control of the hunger mechanism we must know whether to direct the inquiry to the stomach or to the vagi centres in the medulla.

Mr. V. could not be used in this investigation for the reason that his oesophagus is completely closed at the level of the sternum. We have not yet determined whether his lower oesophagus is open. But even if it should prove to be open, there would be considerable difficulty in introducing a balloon through the cardia via the gastric fistula, and it probably would be impossible to keep the balloon there when once introduced, because of the local contractions and peristalsis induced in the oesophagus by the mechanical stimulation from the distended balloon. The work on man was therefore done on the authors themselves, and on a third man, Mr. J. H. L. All three men had previously served as subjects in certain work on the gastric hunger contractions.[1]

We experienced no difficulty in swallowing simultaneously the gastric and the oesophageal balloons with their flexible rubber tube attachments. In part of the work we used best quality of rubber condums also for the oesophagus balloon, not in their entire length as in the case of the stomach, but cut down to a length of 3 to 4 cm. We soon encountered difficulties in the work with the oesophagus, difficulties apparently not noticed by

[1] Carlson: This journal, 1914, xxxiii, p. 95.

Cannon and Washburne, and thinking that part of these difficulties might be due to the diameter of the oesophagus balloon, we resorted to the rubber finger cot employed by these observers. But even the best rubber finger cots are not as satisfactory as the condum balloons.

The position of the balloon in the oesophagus was usually determined by the distance from the incisor teeth to the lower end of the balloon. If the balloon is clear above the cardia the movements of inspiration decrease the positive pressure in the distended balloon in proportion to increase in the negative pressure in the thoracic cavity. But if the balloon is located in the region of the cardia itself it depends on the relative preponderance of diaphragm and chest movements whether the act of inspiration leads to increase or decrease in the balloon pressure. The oesophagus balloon can be well in the cardia and still show negative pressure in inspiration if the inspiration is predominantly costal. On the other hand, if the lower end of the balloon is just within or at the cardiac orifice, a diaphragmatic inspiration increases the pressure in the balloon, although not to the same extent as when the balloon is in the fundus of the stomach.

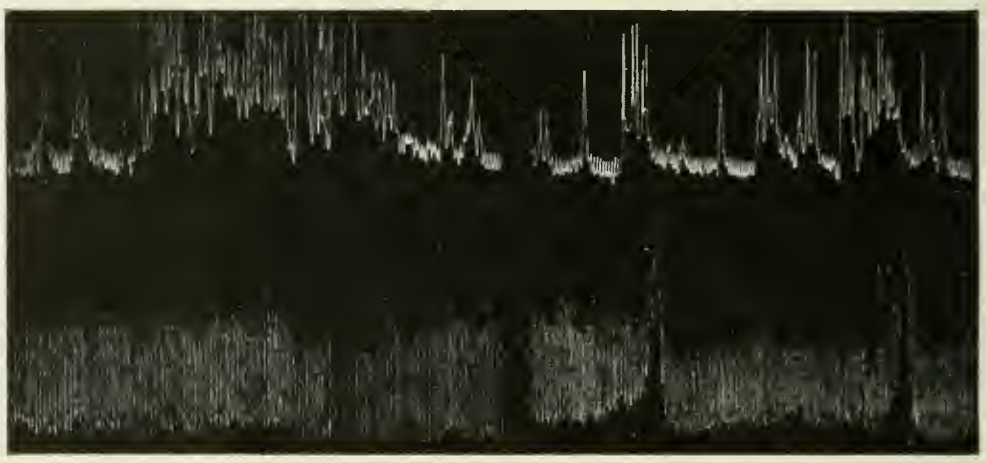
In the case of A. J. C. and J. H. L. it was found that when the distance from the lower end of the oesophagus balloon to the incisor teeth was $15\frac{1}{2}$ to 16 inches the balloon was as far down as it could be located without being directly affected by the contractions of the cardia and the stomach. Allowing the balloon to slip down $\frac{1}{2}$ to 1 inch further brought it in the cardia and the cardiac end of the stomcah. In the case of A. B. L. the distance from the incisor teeth to the lower end of the balloon could not exceed $14\frac{1}{2}$ to 15 inches, if pure oesophagus effects were to be obtained. When the oesophagus balloon is located 14 to 16 inches from the incisor teeth, it is obviously well below the level of the heart, and therefore in the region of myenteric plexus and nonstriated musculature of the oesophagus.

The oesophageal and stomach tubes were usually joined together firmly so that the lower end of the oesophagus balloon was $1\frac{1}{2}$ inches above the upper end of the stomach balloon. The pressure of the oesophagus balloon varied between 1 and 4 cm. of chloroform.

Results in Man

1. Local Contractions and Peristalsis. — When the oesophagus balloon is distended with a pressure of 2 to 4 cm. chloroform the oesophagus usually exhibits rapid continuous contractions. These contractions are at times quite regular both in rate and amplitude. The total time of each contraction is less than two seconds.

In addition to these contractions the oesophagus may show contractions of a tonic character. The duration of these contractions vary from a few seconds to several minutes. If these tonus contractions are only moderately strong, the rapid contractions, just mentioned, continue and are superimposed on



A *B*

Figure 1. (One half the original size.) Simultaneous records from the stomach (lower curve) and lower third of the oesophagus (upper curve) of A. B. L. In *A* the stomach is quiescent; in *B* there is seen the beginning of a period of gastric hunger contractions. The irregular oesophageal contractions are not related to stomach contractions and do not give rise to and are not associated with the sensation of hunger.

the former. In some cases the tonus contractions are quite regular in rate and intensity, but this is the exception. (Figs. 1 and 3.)

Both types of contractions appear to be local. They are not related to oesophageal peristalsis, although a peristalsis (caused by swallowing) may induce them in a quiescent oesophagus. They are not related to gastric contractions, for they occur when the empty stomach is quiescent (Fig. 1.) They may also occur during

gastric hunger contractions, but in this case there is no synchrony between the gastric and the oesophageal contractions. They are local contractions of the oesophageal tube and not peristaltic, because they do not move the distended balloon. But occasional peristaltic contractions of local origin appear during these contractions. This is shown by the pull on the tube if this is fixed to the teeth, or by the downward movement of the tube if it is not fixed. In this way the oesophagus balloon is worked through the cardia unless the tube is secured to the teeth. This peristalsis is obviously identical with the " secondary peristalsis " of Meltzer.

These oesophageal contractions do not give rise to hunger and are in no way associated with this sensation. The rapid contractions do not affect consciousness, but more prolonged tonic contractions are felt if they are strong or moderately strong. They are felt, not as hunger pangs, but as a fullness in the chest or throat, as *something having stuck in the throat.* This sensation is so characteristic and distinct that there is no possibility of confusing it with hunger pangs of gastric origin.

These contractions are caused by the local mechanical stimulation of the distended balloon. The contractions are more marked the greater the pressure in the balloon, but at times they appear even with a balloon pressure of less than 1 cm. chloroform. They are most marked immediately after the introduction and distension of the balloon, but they may persist during an entire observation period of four to five hours if the balloon pressure is above 1 to 2 cm. chloroform. We did not observe any decrease in these local contractions during the progress of the experiments, as one might have expected in case there was any appreciable " education " of the oesophagus to the pressure of the balloon. Evidently the oesophagus mechanisms are so adjusted that local mechanical stimulation causes local contractions interspersed with occasional peristalsis until the stimulus is removed, that is, the material forced into the stomach. The local contractions as well as the secondary peristalsis may be reflexes via the medulla, as indicated by Meltzer's observations. But the absence of the contractions after section of the vagi does not prove it, at least for the part of the oesophagus provided with

non-striated musculature and myenteric plexus. Cannon has shown that this part of the oesophagus responds to local stimulation with local contractions and peristalsis after recovery from the temporary hypotonicity following section of both vagi.[1]

These local contractions of the oesophagus were evidently not encountered by Cannon and Washburne, although the only difference between our technique and theirs is the additional balloon in the stomach (and, in consequence, two rubber tubes in the oesophagus). Is the local excitability of the oesophagus increased by the presence of a distended balloon in the stomach, a rubber tube in the cardia, and a second rubber tube in the oesophagus and mouth? All the men used in our experiments showed these contractions. Can it be the oesophagus of Mr. Washburne is exceptional? Or did Cannon and Washburne have the oesophagus balloon actually located in the cardia, so that their tracings record the behavior of the cardia rather than that of the oesophagus proper?

Boldireff pointed out that the balloon method cannot be used for recording the periodic contractions of the empty intestines, for the reason that the distended balloon causes local contractions through mechanical stimulation. Fortunately this is not true for the gastric fundus. It is true for the oesophagus, at least to an extent to greatly impair the balloon method. For when the oesophagus balloon is distended sufficiently to register the slightest tonus variations and contractions of the oesophagus, the local contractions are most prominent and disturbing.

2. The Contractions Synchronous with the Gastric Hunger Contractions.—The weaker gastric hunger contractions at the beginning of a hunger period are usually not accompanied by any oesophageal contractions (Fig. 2A). But synchronous with the strong hunger contractions that mark the culmination of a gastric hunger period there is some persistent increase in the tonus of the oesophagus and brief contractions simultaneously with the individual stomach contractions (Fig. 3). This increased tonus and rhythmic contractions of the oesophagus parallel with the hunger activity of the empty stomach are in evidence even when the oesophagus exhibits the rapid local contractions

[1] Cannon: This journal, 1906, xvii, p. 586.

described above. The oesophagus contractions appear to lag behind the gastric contractions and are as a rule of briefer duration. This may mean either that the oesophagus contractions are reflexes via the medulla initiated by the stimulation of vagi nerve endings in the stomach, or the delay in the appearance of the contractions may be due to a less sensitive recording apparatus,

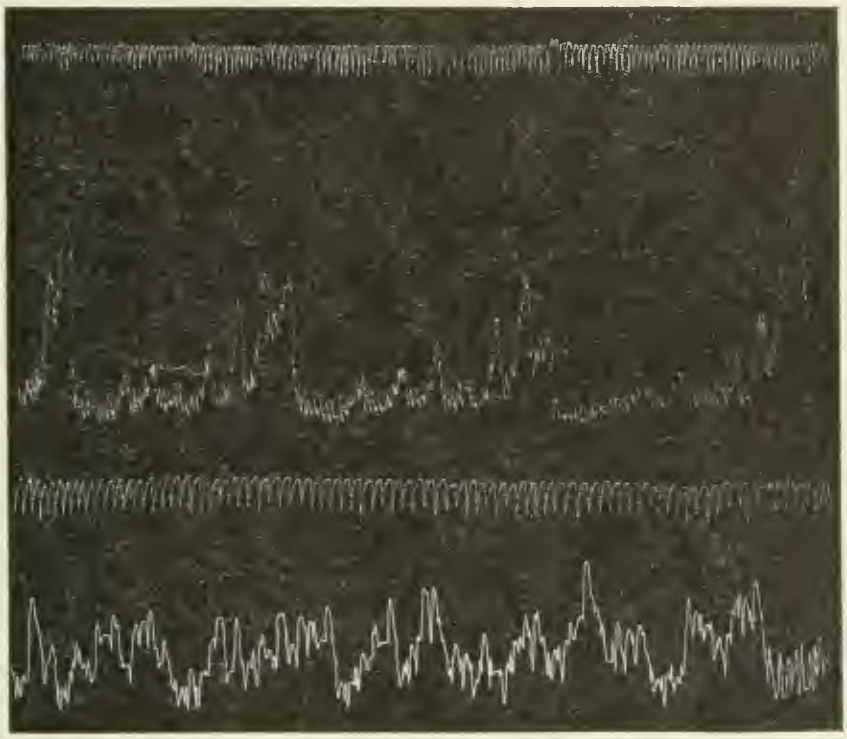


FIGURE 2. (One half the original size.) *A*, simultaneous records from the stomach (lower curve) and lower third of the oesophagus (upper curve) of J. H. L. Pressure in the oesophageal balloon = 2 cm. bromoform. Showing complete quiescence of the oesophagus at the beginning of a period of gastric hunger contractions. *B*, simultaneous record from the stomach and the lower third of the oesophagus in the dog, showing complete quiescence of the oesophagus during moderate gastric hunger contractions.

it being necessary to maintain a slight pressure in the oesophageal balloon in order to eliminate or minimize the local oesophageal contractions. The frequent culmination of the gastric hunger contractions in a period of incomplete tetanus of varying durations seems to have no parallel in the oesophagus in the way of strong and prolonged contractions.

These oesophageal contractions parallel with the gastric hunger contractions are apparently not identical with the oesophageal contractions reported by Cannon and Washburne. These

observers noted that the oesophageal contractions were more prolonged than the gastric contractions of the same man during other hunger periods. The contractions noted by us are usually briefer than the parallel stomach contractions. Washburne was able to associate the oesophageal contractions with the sensation of hunger pangs. None of us are able to do that. In the first

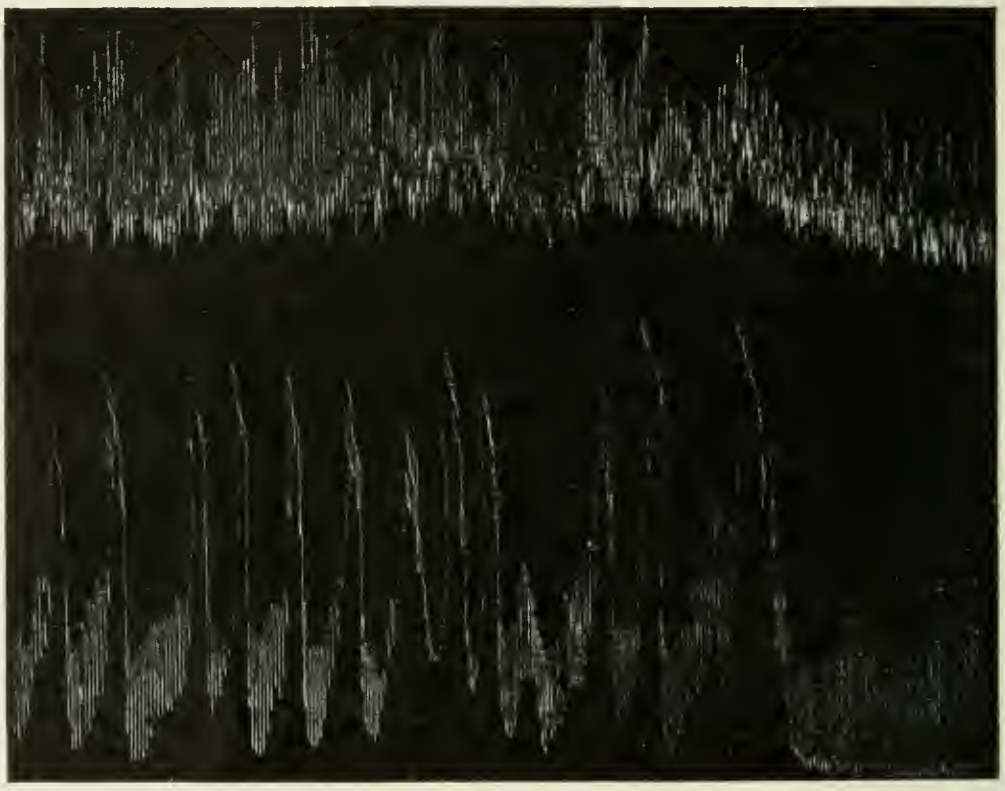


FIGURE 3. (One half the original size.) Simultaneous records from the stomach (lower curve) and the lower fourth of the oesophagus (upper curve) of A. J. C. during the culmination of period of vigorous gastric hunger contractions. Lower end of oesophageal balloon = 16 cm. from incisor teeth, that is, at the cardia. Pressure in balloon = 3 cm. chloroform. Showing weak oesophageal contractions synchronous with the gastric hunger contractions.

place the oesophageal contractions that occur spontaneously during quiescence of the empty stomach contractions that may be identical in rate and strength with those parallel with the gastric hunger contractions are either not felt at all, or else felt as a disagreeable fullness in the throat, something sticking in the oesophagus, and not as the uncomfortable emptiness that characterizes the genuine pangs of hunger. To be sure, when the gastric hunger contractions are sufficiently intense to be

definitely accompanied by oesophageal contractions all three of us feel the pangs of hunger strongly, but these are of gastric origin and are referred to the stomach and not to the oesophagus or throat.

3. Contractions of the Cardia. — That there is an increase of the tonic contraction of the cardia during the gastric hunger contractions is rendered probable by the fact that the air and other gases always present in the stomach are not forced into the oesophagus during these contractions even when very strong. Cannon and Washburne state that this fact argues for contractions of the oesophagus parallel with the contractions of the empty stomach. Did they not overlook the fact that the cardia is capable of doing this even in the absence of oesophageal contractions? There is no escape of air from the stomach during the periods of incomplete gastric tetanus at the end of a hunger period although these tetany periods are usually not accompanied by any oesophageal contractions. There is no escape of air from the dog's stomach during the gastric hunger contractions although these contractions are practically never accompanied by any oesophageal contractions. In the dog oesophageal contractions are known to be permanently abolished by section of both vagi, yet this does not lead to belching of air even during the greatest increase in intragastric pressure that the contractions of the empty stomach are capable of producing.

It is therefore evident not only that cardia itself is able to prevent the escape of air into the oesophagus during intragastric pressure, but also that the cardia in all probability contracts more powerfully during the gastric hunger contractions, thus increasing its efficiency as a guard. Direct graphic evidence of the latter is, however, difficult to secure.

1. When the empty stomach is quiescent the cardia offers only slight resistance to the withdrawal of a distended balloon of the size of a rubber finger cot from the stomach into the oesophagus. The resistance is ordinarily so slight that it seems to be mainly due to friction of the balloon and tube in the oesophagus. A larger balloon, such as the condum used for the stomach, encounters somewhat greater resistance at the cardia, as well as in the oesophagus itself. *If one attempts to withdraw the balloon*

from the stomach at the height of a gastric hunger contraction the resistance offered by the cardia is distinctly increased. This can mean only one thing, viz., an increase in the contraction of the cardia. If the contraction of the cardia did not increase, the withdrawal of the balloon would be actually facilitated by the pressure exerted by the stomach contractions. For example, increasing the intragastric pressure by forcible contraction of the abdominal muscles may force the stomach balloon into the oesophagus in case the stomach is quiescent.

2. It is very difficult to keep an inflated balloon actually in the cardia for any considerable time, especially during the strongest gastric hunger contractions. Strong oesophageal peristaltic movements keep pushing it toward the stomach, and at times the gastric contractions actually push it back into the oesophagus. At the best the balloon will stay in the cardia during two or three successive gastric contractions of the weaker type, that is, at the beginning of a hunger period. The type of balloon used for these tests was the rubber finger cot 3 cm. in length. A balloon of greater length could, of course, be lodged in the cardia with greater ease, but a balloon of greater length than 3 cm. would be influenced not only by the cardia, but also by the cardiac ends of the stomach and the oesophagus. In fact this probably occurs, but to a less extent even when a short balloon is used, as the physiological cardia is probably less than a centimetre in width. Anatomically the cardia is not sharply differentiated in man. We judged the position of the balloon in the cardia by the distance of the balloon from the incisor teeth and by the influence of the respiratory movements, moderate inspiration, mainly costal, causing lowered tension, and moderate diaphragmatic inspiration causing increased tension. When the balloon is in this position the cardia exhibits the 20 seconds rhythm previously reported for the fundus of the empty stomach. This rhythm of the cardia is in evidence even when the empty stomach is quiescent. When the empty stomach shows hunger contractions the cardia shows parallel contractions or periods of increased tonus. The contractions of the fundus and of the cardia are strictly synchronous, but the cardia contractions appear to be more persistent or tetanic. The tracings

secured by us from the balloon in the cardia resemble those published by Cannon and Washburne as oesophageal contractions more than do the actual oesophageal contractions obtained by us.

4. Contractions of the Oral Half of the Oesophagus. — In a few experiments the oesophageal balloon was placed in the oesophagus seven to ten inches from the incisor teeth, that is, in the lower part of the neck and the upper part of the chest. The spontaneous local contractions are in evidence also in this part of the oesophagus. There is usually a slight increase of tonus when very strong gastric hunger contractions are present, but nothing like the strength of contractions during the peristalsis of deglutition or those caused by the local mechanical stimulation. The tonus increase of the upper half of the oesophogus parallel with the gastric contractions is insignificant compared with the corresponding contractions of the lower third of the oesophagus. This is probably correlated with the gradual disappearance of non-striated musculature and myenteric plexus in the oral half of the oesophagus in man.

Results on Dogs

All of our dogs used in this work were provided with a gastric fistula for the introduction of the stomach balloon. The oesophagus was left intact and the oesphageal balloon introduced through the mouth. The dog is of special interest in this connection, because the dog's oesophagus is composed of striated musculature throughout its whole length. The myenteric plexus is probably also lacking. It is needless to say that all the dogs were subjected to preliminary training in the way of getting used to the balloons in stomach and oesophagus. As a matter of fact all the dogs were well accustomed to these procedures having been used for other lines of work on the hunger mechanism, so that they would lie quietly and comfortably in the lap of an attendant during the tests. It is absolutely essential that the dogs are quiet, if possible sleeping, during these tests, for restlessness increases the disturbance of the oesophagus even more than of the stomach.

The same types of balloons were used for dog and man.

1. The Local Spontaneous Contractions. — The presence of the inflated balloon in any region of the oesophagus caused rapid local contractions, more rapid than those of the human oesophagus, alternating with an occasional peristalsis, also of local origin, and occasionally more prolonged tetanic contractions. These tetanic contractions usually last only for half a minute to a

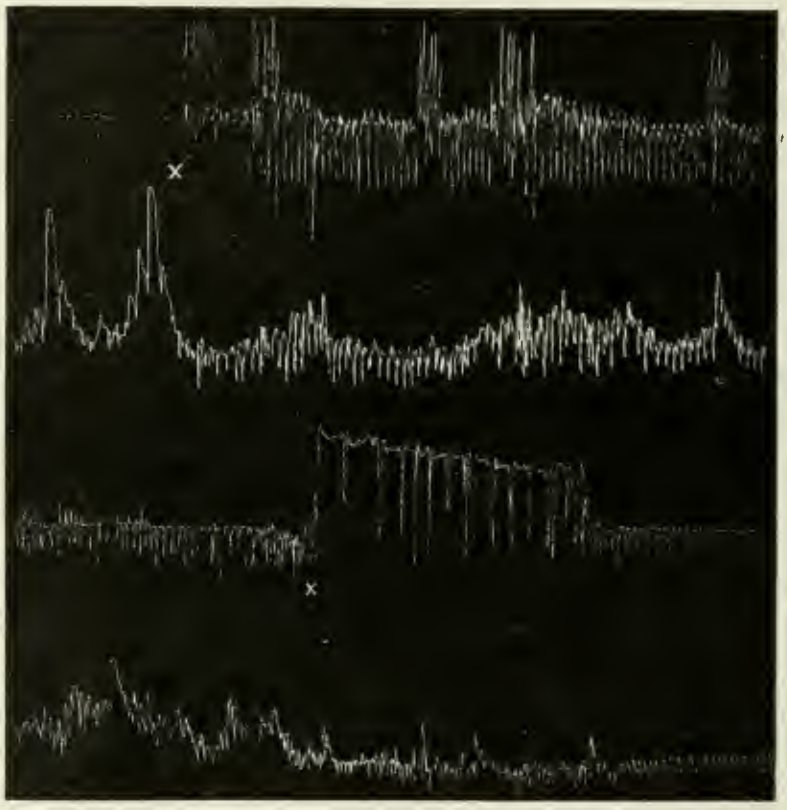


FIGURE 4. (One half the original size.) Simultaneous records from the stomach (lower curve) and the lower third of the oesophagus (upper curve) of the dog. At *X* the dogs were allowed to see and smell meat. Showing initiation of oesophageal contractions parallel with inhibition of the gastric hunger contractions by the sight and smell of food.

minute. In one case they lasted fifteen minutes. Tetanic spasms lasting up to five minutes are not uncommon (Fig. 4B). These contractions have no relation to the hunger contractions of the empty stomach, as they may appear during a hunger period as well as during gastric quiescence (Fig. 5.) They depend on the local stimulation of the balloon in the oesophagus and are therefore more marked the greater the tension in the balloon. They are also more marked when the dogs are excited, evidently owing to increased reflex excitability of the medullary centres and some

increase in the tonus of the oesophagus. The disturbance is greatest when the balloon is first introduced, but it may keep up for hours even when the pressure in the balloon is only 2 to 3 cm. of bromoform or chloroform. A single swallowing act may induce these local contractions, lasting for many minutes, in a quiescent oesophagus. The same thing has been observed in man. It is probably due to increased reflex excitability of the medulla and

FIGURE 5. (One half the original size.) Simultaneous records from the stomach (lower curve) and the lower third of the oesophagus (upper curve) in the dog. Showing periods of rapid oesophageal contractions and weak gastric hunger contractions, but absence of coördination between the two series.

to increased tonus of the oesophagus, as the latter is equivalent to increased tension in the balloon, and therefore increased strength of the local mechanical stimulation.

When the oesophagus contracts in tetanus on the balloon, additional disturbing factors appear. Evidently this kind of contraction causes the same sensation in man and dog, that is, the feeling of something stuck in the throat, for when these contractions are present the dogs become restless and sometimes swallow repeatedly.

2. The Condition of the Oesophagus during Gastric Hunger Contractions. — The gastric hunger contractions are not accompanied by contractions or changes of tonus in any part of the oesophagus (Fig. 2B). If the gastric hunger contractions are very intense so that they cause the dog to moan or swallow, contractions may appear in the quiescent oesophagus, but this is

obviously due to the general disturbance of the animal. There is no synchrony between the gastric and the oesophageal contractions. If the dog lies quietly or is sleeping, a strong gastric hunger period may run its course without the least evidence of oesophageal contractions.

3. Inhibition of the Gastric Hunger Contractions during the Tetanic Contractions of the Oesophagus. — The strong and prolonged local contractions of the oesophagus cause inhibition of the gastric tonus and the gastric hunger contractions, while the rapid oesophageal contractions seem to have no effect on the stomach. This is evidently a special instance of the "law of the intestine," that is, inhibition caudad to a region in the state of contraction. Other factors may also be concerned in this inhibition of the stomach. The tetany of the oesophagus causes some distress, and this may lead to inhibitory action via the splanchnic nerves. The gastric inhibition ordinarily lasts as long as the tetanus in the oesophagus.

4. The Contraction of the Oesophagus in Response to Seeing and Smelling Food. — Seeing and smelling meat on the part of a hungry dog almost invariably lead to contractions of the otherwise quiescent oesophagus. Ordinarily the contractions are of the local rapid type and the disturbance of the oesophagus lasts only for 10 to 30 seconds. But occasionally the sight or smell of food may send the oesophagus into complete tetanus lasting for several minutes. Both types of oesophageal contractions are accompanied by inhibition of the stomach (Fig. 4). A single act of swallowing, as we have seen, may produce the same disturbance in the part of the oesophagus where the balloon is located, and the dog frequently swallows or at least elevates the larynx at the sight of food. But these contractions on the sight of food also appear when the dog does not swallow. The phenomenon is probably to be explained as follows: The sight or smell of food on the part of the hungry dog causes temporary increase in neuro-muscular tonus, including the tonus of the oesophagus. The increase in oesophagus tonus causes greater pressure on the balloon, and in consequence stronger mechanical stimulation of the afferent nerves in the oesophagus, and hence the rapid or tetanic contractions. It is therefore probable that the actual

contractions of the oesophagus on seeing food are artifacts, so to speak, due to the presence of the balloon.

These tests were made with the view of determining whether peripheral factors enter into the apparent augmentation of hunger (?) and appetite by the sight and smell of food. It has been reported that tasting or chewing palatable food in man inhibits the hunger contractions, and in dogs the same inhibition, although more temporary, follows the sight and smell of food.

Our tests show that the sight and smell of food on the part of the hungry dog cause a temporary increase in the tonus of the oesophagus. But since almost any kind of disturbance of the dog does the same thing, we question whether this fact is of significance in the influence on appetite of seeing or smelling food on the part of a hungry animal.

These results on man and dog support the view that the gastric (and oesophageal) hunger contractions are primarily of local origin or automatic rather than initiated by discrete motor impulses through the vagi. It seems probable that these hunger periods are also accompanied by increased vagus tonus, automatic or reflex, but actual proof of this is yet lacking. The gastric hunger contractions in man are accompanied by contractions only of that part of the oesophagus containing myenteric plexus and smooth musculature. The dog's oesophagus contains no nonstriated musculature and no myenteric plexus and there are no oesophageal contractions parallel with the gastric hunger contractions. These facts suggest that the coördination of the hunger contractions of the stomach and the lower end of the oesophagus in man is a function of the myenteric plexus. We had hoped to prove this definitely in cats by section of the vagi in the chest, the cat's oesophagus resembling that of man in distribution of nervous and muscular tissues. But the cat is so greatly annoyed by the oesophageal balloon, that satisfactory data cannot be obtained, except possibly after long training.

Boldireff found that the intestines (presumably both the large and small intestine) exhibit rhythmic contractions during the periods of gastric hunger contractions. His evidence consisted of the sound produced by the moving gas in the intestine and the appearance of the free end of the fistula of the small intes-

tine. More accurate methods of registration must be devised. Rumbling intestinal sounds may be heard when the stomach is quiescent. These are probably due to local stimulation owing to distension by the gases, hence mostly confined to the large intestine. Rumbling intestinal sounds are usually heard during gastric hunger periods, and it seems to us, one can at times actually feel the intestinal movements. If this is the case, the intestinal hunger movements must be much more vigorous than the digestive movements. The character of the intestinal hunger contractions is not known. Do they consist in peristalsis, in segmentation, or in pendulum movements? Or is it a type of contraction not seen during digestion: rhythmic contractions and relaxations throughout the whole intestine and synchronous with the systole and diastole of the hunger beats of the stomach and the lower end of the oesophagus? This would imply a type of coördination of the neuro-muscular mechanism of the entire digestive tract not revealed by the movements of digestion. In the movements of digestion the oesophagus, the cardia, the fundus, the antrum pylori, the pyloric sphincter, and the intestines act as relatively independent mechanisms and appear to be governed by laws of their own in harmony with the role played by these regions in digestion.

While we admit the possibility that the contracting oesophagus and intestines may contribute to the sensation of hunger, this contribution is of minor importance in comparison with that of the stomach. The hunger pangs run absolutely parallel with the gastric hunger contractions, only lagging some seconds both at the beginning and the end of the contractions. A strong contraction artificially induced in the empty stomach is recognized as a hunger pang; a similar contraction induced in the oesophagus when the stomach is empty is recognized as something quite different from hunger. And this will in all probability prove to be true also of the intestine.

ON THE CAUSE OF CONGENITAL GOITRE (THYROID HYPERPLASIA) IN DOGS AND CATS[1]

By A. J. CARLSON

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THE starting point of this investigation was some observations, incidental to other work on the thyroid, that pups from mothers with active thyroid hyperplasia seemed to have much larger thyroids than pups from mothers with normal thyroids or with colloid goitre. Several litters of pups seemed to show that the young of mothers with active thyroid hyperplasia are born with goitre, while mothers with colloid goitres give birth to young with normal thyroids. It is well known that goitre in dogs may be considered endemic in Chicago and the Great Lakes region.[2] It seemed to the writer that some questions of importance in thyroid physiology and pathology might be brought a step nearer solution if it could be shown that in this region of endemic goitre the young are born with normal thyroids, unless the mother has thyroid hyperplasia during gestation, and that in the latter case the offspring always shows thyroid hyperplasia. Accordingly, the gathering of material on these points began in the spring of 1912, and up to date we have secured data on 45 mothers and 250 pups. Material was also gathered on cats, especially in view of the fact that cats are much less subject to pathological changes of the thyroids than dogs. The cat material comprises 26 mothers and 112 kittens. Since all the results are consistent, it seems that the material at hand is sufficient for presentation.

[1] A preliminary report on some of the data in this paper appeared in Proceedings of the society for experimental biology and medicine, 1913, x, p. 185.

[2] MARINE: Johns Hopkins Hospital bulletin, 1907, xviii, p. 359; Archives of internal medicine, 1908, i, p. 349, iii, p. 66, iv, p. 440; CARLSON and WOELFEL: American journal of physiology, 1910, xxvi, p. 32.

The Diagnosis of the Maternal Thyroids. — In dogs there is no difficulty in distinguishing the three types of thyroid: normal, colloid, and hyperplastic, when the colloid or hyperplasia is marked. But normal glands vary in the size of acini and quantity of colloid, so that in many cases it is a question whether the gland is to be classed as normal or as moderate colloid. It is probable that several of the thyroids designated as normal by me would have been placed in the colloid group by Marine, as his percentage of normal thyroids in dogs is much smaller than ours. But the grouping of doubtful cases with the normal or with the colloid is of no importance here for the reason that mothers with colloid goitre give birth to young with normal thyroids. Marine and Lenhart distinguish seven classes of hyperplastic thyroids in dogs.[1] There is no difficulty of recognizing slight, moderate, and extreme hyperplasia, but there are all gradations between these three groups. All hyperplastic thyroids are therefore arranged in one group, since the difference between them is only one of degree, at least so far as can be determined by ordinary staining methods.

None of the cats had thyroids that could be classed as colloid. And the cat thyroids that are designated as hyperplastic differ considerably from the type of hyperplasia so characteristic in dogs and man. Polymorphic acini were never seen in cats. But the maternal thyroids classed as hyperplastic showed a decreased number of acini, decrease in colloid, change of the cells from the cuboidal to the columnar type, and a marked increase of cells between the acini. This hyperplasia in cats is probably similar to the thyroid hyperplasia of pregnancy so frequent in women.

The thyroids were freed from extraneous connective tissue as much as possible, weighed, and fixed in 4% formalin. When pups or kittens were taken from the uterus, the weight of the young was always deducted from the total weight of mother and young.

There are obvious unavoidable sources of error in the thyroid weight-body weight ratios as determined in this work. In the first place, the animals differ in the amount of adipose tissue.

[1] Marine and Lenhart: Archives of internal medicine, 1909, iii, p. 67.

There is no evidence that the thyroid increases or decreases proportionately with the gain or loss of body fat. There is also an error from variations in the amount of accessory thyroids. Accessory thyroids are of frequent occurrence in dogs. This source of error must also be reckoned with in the young. The variation in age of the young is also a factor. Jackson has shown for man that the total body weight increases faster than the thyroid weight during intrauterine life, so that the body weight-thyroid weight ratio is gradually increasing.[1] This seems to be the situation in dogs and cats also. We aimed to take the material at birth or a day or two after birth. But street dogs kept under laboratory conditions may not all retain their young until full term. In the few cases where pups or kittens were taken from the mother, the mother being used in connection with other work, this is indicated in connection with each litter. The error in variations in age of the offspring might have been reduced by excluding all the data on litters not of full term. But the reader can easily satisfy himself that the exclusion of that material does not essentially alter the results.

As was noted, these sources of error are obvious but practically unavoidable, except in so far as their influence on the general average is largely neutralized on account of the great number of cases in each group. This was one of the reasons for collecting the quantity of material here presented. Moreover, the actual thyroid weight-body weight ratio is of minor significance in the case of the mothers. In the mothers the all-important factor appears to be the physiological state of the thyroid. It is the degree of hyperplasia and not the size of the gland that runs parallel with the character of the thyroids of the offspring. In the young the actual weight of the thyroid is of greater significance than in the mother, but we shall see that the thyroids of the offspring from hyperplastic mothers have other distinguishing characters besides that of increased bulk.

In the general summaries (Series I–V) only the average body weight and thyroid weight of each litter are given. The degree

[1] Jackson: American journal of anatomy, 1909, ix, p. 133.

of thyroid variation in individuals of the same litter will be considered later.

We now invite attention to the summaries of the material in the different groups.

DOG. SERIES I

MOTHERS WITH THYROIDS OF NORMAL OR NEARLY NORMAL STRUCTURE

Dog	Body weight	Thyroid wt. gr.	Ratio	Character of thyroid
1 Mother	10.0 K.	2.75	1–3600	Normal
5 pups at birth	216 gr.	0.07	1–3100	Acini, some colloid
2 Mother	10.0 K.	1.5	1–6600	Normal
4 pups at birth	184 gr.	0.09	1–2000	Acini, trace of colloid
3 Mother	5.5 K.	0.90	1–6100	Normal
4 pups at birth	200 gr.	0.045	1–4400	Acini with colloid
4 Mother	9.5 K.	1.46	1–6500	Normal
7 pups at birth	220 gr.	0.08	1–2750	Acini with colloid
5 Mother	14.0 K.	5.0	1–2800	Normal
2 pups before term	20 gr.	0.008	1–2500	No acini or colloid
6 Mother	18.6 K.	3.84	1–4800	Normal
10 pups before term	153 gr.	0.075	1–2000	Acini, trace of colloid
7 Mother	7.35 K.	1.0	1–7350	Normal
3 pups 6 days old	187 gr.	0.049	1–3800	Acini with colloid
8 Mother	11.8 K.	3.54	1–3300	Normal
8 pups at birth	209 gr.	0.047	1–4400	Acini with colloid
9 Mother	9.5 K.	1.85	1–5130	Normal
6 pups at birth	215 gr.	0.10	1–2150	Acini with colloid

Average	9 mothers	49 pups
Body weight	9.7 K.	178 gr.
Thyroid weight	2.43 gr.	0.071 gr.
Ratio	1–4000	1–2500

DOG. SERIES II

MOTHERS WITH COLLOID GOITRE OR CONNECTIVE TISSUE HYPERPLASIA

	Dog	Body weight	Thyroid wt. gr.	Ratio	Character of thyroid
10	Mother	12.9 K.	7.6	1–1600	Colloid
	5 pups at birth	246 gr.	0.085	1–2900	Acini and colloid
11	Mother	13.0 K.	7.0	1–1860	Colloid
	6 pups before term	184 gr.	0.09	1–2040	Outline of acini, no colloid
12	Mother	9.0 K.	3.3	1–2800	Slight colloid
	6 pups before term	51 gr.	0.03	1–1700	Acini with colloid
13	Mother	10.0 K.	2.7	1–3700	Colloid
	4 pups before term	166 gr.	0.09	1–1840	Outline of acini, no colloid
14	Mother	6.0 K.	3.00	1–2000	Connective tissue hyperplasia
	3 pups before term	200 gr.	0.10	1–2000	Acini, some colloid
15	Mother	10.0 K.	5.0	1–2000	Colloid
	3 pups 20 days old	780 gr.	0.35	1–2220	Acini with colloid
16	Mother	19.1 K.	3.68	1–5220	Colloid, excess. con. tissue
	7 pups before term	82 gr.	0.03	1–2730	Acini, no colloid
17	Mother	7.00 K.	7.0	1–1000	Colloid, excess. con. tissue
	6 pups at birth	133 gr.	0.06	1–2200	Acini with colloid
18	Mother	9.2 K.	9.2	1–1000	Colloid
	4 pups at birth	160 gr.	0.08	1–2000	Acini with colloid
19	Mother	7.44 K.	38.0	1–195	Colloid, excess. con. tissue
	4 pups 3 days old	174 gr.	0.07	1–2500	Acini with colloid
20	Mother	14.0 K.	8.5	1–1300	Colloid
	8 pups at birth	295 gr.	0.07	1–4200	Acini, trace of colloid
21	Mother	8.5 K.	5.4	1–1600	Colloid
	5 pups 3 days old	210 gr.	0.06	1–3500	
22	Mother	9.3 K.	5.5	1–1670	Colloid
	5 pups at birth	163 gr.	0.08	1–2040	Acini, trace of colloid
23	Mother	13.64 K.	6.0	1–2270	Colloid
	8 pups at birth	250 gr.	0.10	1–2500	

Average	14 mothers	75 pups
Body weight	10. 6 K.	222 gr.
Thyroid weight	8.0 gr.	0.099 gr.
Ratio	1–1325	1–2230

DOG. SERIES III

MOTHERS WITH THYROID HYPERPLASIA

Dog	Body weight	Thyroid wt. gr.	Ratio	Character of thyroid
24 Mother 6 pups 2 days old	6.5 K. 182 gr.	6.0 0.18	1–1033 1–1000	Slight hyperplasia Outline of acini, no colloid
25 Mother 8 pups at birth	26.0 K. 254 gr.	12.0 0.346	1–2166 1–734	Marked hyperplasia Acini, no colloid
26 Mother 5 pups before term	14.7 K. 205 gr.	23.0 0.254	1–639 1–807	Marked hyperplasia Outline of acini; no colloid
27 Mother 11 pups 2 days old	19.8 K. 375 gr.	4.5 0.31	1–4400 1–1124	Slight hyperplasia Acini, no colloid
28 Mother 5 pups at birth	10.4 K. 270 gr.	12.5 0.33	1–832 1–710	Marked hyperplasia Irregular acini; no colloid
29 Mother 4 pups 3 days old	13.6 K. 275 gr.	4.35 1.32	1–3100 1–208	Extreme hyperplasia Irregular acini, no colloid
30 Mother 7 pups at birth	15.2 K. 357 gr.	15.4 0.37	1–1000 1–964	Marked hyperplasia Irregular acini, no colloid
31 Mother 3 pups at birth	13.5 K. 280 gr.	4.3 0.17	1–3141 1–1680	Slight hyperplasia Acini, no colloid
32 Mother 3 pups at birth	6.2 K. 177 gr.	3.0 0.20	1–3000 1–885	Moderate hyperplasia Irregular acini, no colloid
33 Mother 5 pups before term	16.0 K. 109 gr.	7.17 0.08	1–2231 1–1322	Slight hyperplasia No acini or colloid
34 Mother 8 pups 6 days old	12.0 K. 535 gr.	3.0 0.563	1–4000 1–950	Marked hyperplasia No colloid
35 Mother 6 pups at birth	11.0 K. 375 gr.	22.0 0.55	1–500 1–675	Extreme hyperplasia Irregular acini, no colloid
36 Mother 8 pups at birth	16.3 K. 200 gr.	3.35 0.16	1–4600 1–1240	Slight hyperplasia, colloid Acini and colloid
37 Mother 8 pups before term	11.5 K. 52 gr.	6.6 0.051	1–1744 1–1000	Slight hyperplasia, colloid No acini
38 Mother 6 pups 2 days old	12.36 K. 282 gr.	5.0 0.17	1–2410 1–1660	Slight hyperplasia, colloid Acini and colloid
39 Mother 7 pups 3 days old	8.95 K. 270 gr.	7.0 0.50	1–1280 1–540	Extreme hyperplasia Acini, some colloid
40 Mother 4 pups before term	8.8 K. 148 gr.	5.5 0.116	1–1600 1–1280	Slight hyperplasia, colloid No acini

DOG. SERIES III — *Continued*

Mothers with Thyroid Hyperplasia

41	Mother 2 pups 2 days old	10.6 K. 215 gr.	25.0 0.635	1–424 1–338	Marked hyperplasia Irregular acini, no colloid
42	Mother 7 pups at birth	12.2 K. 176 gr.	82.0 0.33	1–148 1–533	Marked hyperplasia Irregular acini, no colloid
43	Mother 4 pups at birth	10.4 K. 400 gr.	9.0 0.80	1–1100 1–480	Extreme hyperplasia Irregular acini, no colloid
44	Mother 6 pups before term	12.0 K. 150 gr.	6.0 0.18	1–200 1–1200	Slight hyperplasia, colloid
45	Mother 7 pups at birth	15.7 K. 270 gr.	7.7 0.85	1–2000 1–350	Marked hyperplasia Acini, trace of colloid

Average	22 mothers	126 pups
Body weight	12.6 K.	257 gr.
Thyroid weight	10.0 gr.	0.39 gr.
Ratio	1–1260	1–660

CAT. SERIES IV

Mothers with Normal Thyroids

	Cat	Body weight	Thyroid wt. gr.	Ratio	Character of thyroid
1	Mother 4 kittens before term	2.9 K. 75 gr.	0.30 0.012	1–9600 1–6000	Normal
2	Mother 5 kittens at birth	3.0 K. 125 gr.	0.25 0.022	1–12000 1–6500	Normal
3	Mother 6 kittens before term	3.2 K. 92 gr.	0.25 0.015	1–13000 1–6000	Normal
4	Mother 2 kittens before term	2.2 K. 92 gr.	0.25 0.020	1–8800 1–4700	Normal
5	Mother 2 kittens at birth	3.2 K. 110 gr.	0.20 0.015	1–16200 1–7300	
6	Mother 5 kittens before term	2.8 K. 66 gr.	0.20 0.015	1–14000 1–4500	Normal
7	Mother 4 kittens before term	4.6 K. 41 gr.	0.24 0.015	1–16000 1–2800	Normal

CAT. SERIES IV — *Continued*

Cat	Body Weight	Thyroid Wt. gr.	Ratio	Character of thyroid
8 Mother	3.1 K.	0.19	1–15000	Normal
4 kittens before term	56 gr.	0.013	1–4312	Acini, some colloid
9 Mother	2.8 K.	0.23	1–10800	Normal
5 kittens before term	41 gr.	0.01	1–4100	
10 Mother	2.85 K.	0.132	1–19000	Normal
5 kittens at birth	100 gr.	0.017	1–6000	Acini with colloid
11 Mother	3.1 K.	0.25	1–12400	Normal
4 kittens 2 days old	102.5 gr.	0.025	1–4000	Acini with some colloid
12 Mother	3.2 K.	0.25	1–12400	Normal
6 kittens at birth	84 gr.	0.013	1–6720	Acini with some colloid
13 Mother	3.6 K.	0.40	1–9000	Normal
6 kittens 2 days old	110 gr.	0.021	1–5200	Acini with some colloid
14 Mother	3.1 K.	0.25	1–12400	Normal
4 kittens at birth	102.5 gr.	0.025	1–4000	Acini with some colloid
15 Mother	3.2 K.	0.25	1–12400	Normal
6 kittens at birth	84 gr.	0.013	1–6720	Acini with some colloid
16 Mother	2.2 K.	0.28	1–7992	Normal
5 kittens at birth	105 gr.	0.025	1–4200	Acini with some colloid
17 Mother	2.5 K.	0.30	1–8038	Normal
2 kittens at birth	56 gr.	0.014	1–3862	Acini, some colloid
18 Mother	2.5 K.	0.20	1–12500	Normal
2 kittens at birth	108 gr.	0.024	1–4500	
19 Mother	3.5 K.	0.21	1–16600	Normal
5 kittens at birth	102 gr.	0.020	1–5040	Acini, some colloid
20 Mother	2.4 K.	0.23	1–9800	
3 kittens before term	65 gr.	0.017	1–4300	

Average . . . . . 20 mothers . . . . . 85 kittens

Body weight . . . . . 3.0 K. . . . . 80 gr.

Thyroid weight . . . . 0.25 gr. . . . . 0.017 gr.

Ratio 1–12000 1–4705

CAT. SERIES V

MOTHERS WITH THYROID HYPERPLASIA

Cat	Body weight	Thyroid wt. gr.	Ratio	Character of thyroid
21 Mother	3.0 K.	0.45	1–6000	Marked hyperplasia
4 kittens at birth	125 gr.	0.06	1–2000	
22 Mother	3.2 K.	0.40	1–8000	Slight hyperplasia
6 kittens before term	44 gr.	0.015	1–2940	
23 Mother	3.5 K.	0.75	1–4600	Marked hyperplasia
5 kittens before term	40 gr.	0.020	1–2000	
24 Mother	3.2 K.	0.47	1–6700	Slight hyperplasia
6 kittens before term	52 gr.	0.015	1–3400	
25 Mother	2.9 K.	0.43	1–6740	Marked hyperplasia
3 kittens at birth	125 gr.	0.048	1–2605	No acini or colloid
26 Mother	2.2 K.	0.25	1–8800	Slight hyperplasia
3 kittens before term	97 gr.	0.041	1–2300	Outline of acini, no colloid

Average	6 mothers	27 kittens
Body weight	3.0 K.	80 gr.
Thyroid weight	0.47 gr.	0.033 gr.
Ratio	1–6400	1–2424

GENERAL SUMMARY

DOGS

	Body thyroid-weight ratio
From 9 mothers with normal thyroids, 49 pups	1–2500
From 14 mothers with colloid goitre, 75 pups	1–2200
From 22 mothers with thyroid hyperplasia, 126 pups	1–660

CATS

From 20 cats with normal thyroids, 85 kittens	1–4700
From 6 cats with thyroid hyperplasia, 27 kittens	1–2400

The material seems to warrant the following conclusions:

1. The weight and histological character of the thyroids of newly born pups of mothers with colloid goitre are practically identical with those of pups from mothers with normal thyroids. The average ratio in the former group is 1–2200; in the latter 1–2500. In both groups there is considerable development of acini with some colloid at birth.

2. Pups from mothers with active thyroid hyperplasia have thyroids larger than normal in direct proportion to the degree of hyperplasia in the mother. These enlarged thyroids of the pups also exhibit retarded development of acini and colloid, and in cases of extreme hyperplasia in the mother the pup's thyroids give some indication of polymorphic acini formation similar to that in the mothers.

3. Kittens from mothers that have thyroid hyperplasia show thyroid enlargement and retarded formation of acini and colloid similar to that in the goitre pups.

4. All the individuals in litters from mothers with thyroid hyperplasia show the thyroid enlargement and the retarded development of acini and colloid. And no single individual in litters from mothers with normal thyroids or colloid goitre shows thyroids of size and histological character similar to the thyroids of the young from hyperplastic mothers. There are, to be sure, some individual variations in the size of thyroids in members of the same litter, just as there are variations in size of the pups and kittens, but the individual variations are always within the range of the group, except in the case of pups from mothers with very slight hyperplasia. The thyroids in such litters may show individual variations that bring them into the normal or colloid group. This is to be expected when the maternal hyperplasia is very slight. The point of importance is the normal character of the thyroids of all individuals in litters from mothers with normal thyroids or colloid goitre, and the increased size and altered character of the thyroid of every individual in the litter from mothers showing moderate to extreme thyroid hyperplasia.

The variations in size of the thyroids in individuals of the same litter may be partly due to variation in the quantity of accessory thyroid tissue, and hence only apparent. It is not practicable to pick out small accessory thyroids from the thymus tissue and lymph glands in the neck and chest of the newborn pup and kitten. But part of the difference is probably real, and essentially hereditary, that is, due to the same factors that lead to variations in the total body weight in individuals of the same litter. That is to say, there are individual variations in

mass or growth potential of the thyroid anlage in members of the same litter, but the thyroid anlage responds alike to the condition of the thyroid hyperplasia of the mother, for the individual variations of thyroid size in the same litter are, on the whole, not greater in the litters of goitre pups than in the litters of normal pups. The isthmus of thyroid tissue connecting the two thyroid lobes appears to be more frequent in the goitre litters.

5. The normal thyroid in cats is very constant in size and structure, and, in proportion to body weight, about three to four times smaller than the normal thyroids in dogs. The same comparison applies also to the thyroids of the newborn of these two species. Thyroid hyperplasia in cats is also very much less common and less marked than in dogs.

The 126 pups of Series III and the 27 kittens of Series V had congenital goitre. Goitre in the newborn may be due to some temporary abnormal condition of the mother, or it may be inherited, that is, due to defects in the maternal or paternal germplasm. That the congenital goitre under consideration is not hereditary or due to defects in the germplasm seems to be shown by the following facts. Although Chicago is an endemic goitre region for dogs, mothers with normal thyroids never gave birth to goitrous offspring, and mothers that had thyroid hyperplasia but have reverted to the colloid type never gave birth to goitrous offspring. By the law of chance there should at least be an occasional goitrous individual in the litters from normal or colloid goitre mothers in case this congenital goitre is hereditary or due to defects in the germ cells. By the same law of chance the litters from mothers with active thyroid hyperplasia during the gestation should contain at least an occasional individual with normal thyroids. I do not mean to imply that congenital goitre may not under any circumstances result from defects in the germplasm. It is clear, however, that the congenital goitre under consideration is not hereditary. It is obviously due to the *environment*, and the only environment that can act on the mammalian fetus is the maternal blood. *This goitre of the newborn is due to some pathological condition of the maternal blood.* The suggestion is obvious that this path-

ological condition of the maternal blood is also responsible for the thyroid hyperplasia in the mother.

The data on congenital goitre in man are not conclusive on this point and for obvious reasons. Unless the thyroids of the newborn child are sufficiently enlarged to be palpable they would not be recognized as goitre. And samples of the mother's thyroids at the birth of the child can be obtained only under exceptional circumstances. Yet, many cases of goitre in the newborn are on record. In some cases the goitre has been large enough to interfere with delivery of the child. But the correlation between these congenital goitres and the physiological state of the thyroid of the mother is not yet established, although cases are reported of mothers giving birth to children with normal thyroids, and after developing goitre, to goitrous infants. It appears to be a fact, however, that active thyroid hyperplasia in children from one to three years of age is rather uncommon even in goitre districts.

It seems well established that in goitre districts the children's thyroids are in general much larger than in non-goitre districts.[1] It is to be hoped that all human material bearing on this question will be recorded, that is, the cases where the thyroid data, both of mother and child, are available.

What is the temporary pathological condition of the maternal blood that induces this thyroid hyperplasia in the fetus? Is it a condition of hypothyroidism in the mother, so that the thyroid hyperplasia in the fetus is to be explained as a compensatory hypertrophy? Eighteen years ago Halsted removed one half to three fourths of the thyroids in three pregnant bitches. The pups born from these bitches had thyroids twelve to twenty times larger than the thyroids of pups from normal mothers.[2] These enlarged thyroids had no colloid, in fact exhibited a structure similar to the parathyroids. It seems from Halsted's description that the histological appearance of these enlarged fetal thyroids was identical with that of the enlarged thyroids of our pups and kittens from mothers with thyroid hyperplasia,

[1] Isenschmid: Frankfurter Zeitung für Pathologie, v, p. 205; Pollak: Jahrbücher für Kinderheilkunde, 1912, lxxxvi, p. 81.

[2] Halsted: Johns Hopkins Hospital bulletin, 1896, i, p. 399.

that is, a retardation of acini and of colloid formation. Halsted interpreted his results as compensatory hyperplasia. Most of the investigators who have repeated Halsted's experiments have obtained similar, but in no case so marked results.[1] And recently Halsted has obtained results which seem to show that the hyperplasia of the maternal and fetal thyroids after partial thyroidectomy of the mother is due to infection and not to a condition of hypothyroidism of the mother.[2] In view of these facts it is clear that the effect on the fetus of hypothyroidism of the mother is still an open one.

Does the so-called "experimental hyperthyroidism" throw any light on the cause of the congenital goitre? Some investigators have studied the influence on the fetus of excessive thyroid feeding of the mother during pregnancy, assuming that thyroid feeding results in physiological hyperthyroidism. This assumption is not well founded.[3] Bleibtreu fed thyroids to pregnant rabbits and reports disturbances of pregnancy (abortion, death, absorption of fetus).[4] Hoskins fed thyroid preparations to pregnant guinea pigs and found that the newborn had abnormally small thyroids. They had also small adrenal glands and ovaries, while the thymus was enlarged. The structure of the thyroids was practically normal.[5] We cannot accept these results as due simply to hyperthyroidism. Commercial thyroid preparations are toxic, affecting many if not all organs of the body. Gudernatsch has recently shown (on tadpoles) that thyroid feeding arrests growth and accelerates tissue differentiation and metamorphosis.[6] Cramer and Krause find that thyroid feeding destroys the capacity of the liver to store gly-

[1] Edmunds: Lancet, 1901, i, p. 1451; Hunt: Journal of the American medical association, 1907, xlix, p. 1326; Marine and Lenhart: Archives of internal medicine, 1909, v, p. 268; Lanz: Beiträge zur klinischen Chirurgie, 1909, xlii, p. 420.

[2] Halsted: Proceedings of the Society for experimental biology and medicine, 1913, x, p. 185.

[3] Carlson, Rooks, and McKie: This journal, xxx, 1912, p. 129.

[4] Bleibtreu: Deutsche medicinische Wochenschrift, 1907, xxxiii, p. 15.

[5] Hoskins: This journal, 1910, xxvi, p. 426.

[6] Gudernatsch: Archiv für Entwickelung-Mechanik der Organismen, 1912, xxx, p. 457.

cogen, without increasing sugar oxidation. Disturbances in the protein metabolism were also noted.[1] It is obvious that the results of thyroid feeding are so complex that the effect on the fetus or on the fetal thyroids of excessive thyroid feeding of the mother during gestation can as yet not be interpreted as due simply to hyperthyroidism of the mother.

Are our results consistent with the view that all thyroid hyperplasia is compensatory? This question cannot be answered at present. We must first know what happens to these congenital goitres after birth. Will they continue to show thyroid disturbances through life? Will the hyperplasia persist as long as the young suckle their mother? Will it be arrested by giving the young a normal wet nurse? We must know whether we can arrest the development of the fetal thyroids by physiological hyperthyroidism of the mother and *vice versa*. The pathological condition of the maternal blood that causes thyroid hyperplasia in the fetus is evidently a stimulus to growth with accompanying retardation of thyroid differentiation and not a stimulus to thyroid secretion. *Thyroid hyperplasia may therefore lead to or cause hypothyroidism rather than be the result of hypothyroidism.*

I have seen young dogs (two to four months old) that in all probability belonged to the group of congenital goitre, although I am not certain on that point, as in each case I was unable to trace the mother, or other members of the litter. These pups had very large and hyperplastic thyroids, but had also the appearance of *cretins:* retarded growth, defective hair growth, thick and dry skin, weakness, pot belly, and they were stupid and lethargic. Two of these showed distinct improvement on thyroid feeding. A third pup, probably four months old, had extremely hyperplastic thyroids, weighing 170 gr. One and one half lobes of the thyroids were removed aseptically. This was followed by very rapid improvement until two months after the operation the dog seemed practically normal. There had been no improvement in the dog during five weeks in the laboratory prior to the operation. There was no change in diet or care of the dog. The improvement of the dog was noticeable

[1] Cramer and Krause: Proceedings of the Royal Society, 1913, lxxxvi, B, p. 550.

shortly after the operation. Yet we may not conclude that the removal of a greater part of the thyroid caused the improvement. This is only one case and the improvement may have been a coincidence. If it was not a coincidence, it is obvious that thyroid hyperplasia is more complex than mere compensatory hypertrophy.

THE VENOUS PULSE

By EPHRAIM M. EWING

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DESPITE the fact that venous pulse tracings have been so widely used to supplement the diagnosis of cardiac arrhythmias by the ordinary methods, there is still considerable diversity of opinion as to the times of occurrence and causes of the waves in the phlebogram. Concerning only one wave, the first positive or auricular, is there unanimity of opinion. In the case of the second positive (Mackenzie's "c") wave, some hold that it originates within the heart, while others believe that it results simply from impact of the carotid artery against the jugular vein. There is still greater disagreement concerning the third positive (Mackenzie's "v") wave. Some investigators consider that it occurs at about the middle of ventricular systole, while others place it in diastole; naturally, there can be no agreement as to its manner of origin.

With these points in mind, the present investigation has been carried out first with the idea of accurately determining the time relations existing between all the waves in the venous pulse and the events in the cardiac cycle, and secondly, deducing from such data the manner of origin of the various waves.

While each of the waves is discussed in detail, emphasis is placed on the consideration of the first onflow and diastolic waves, (corresponding to Mackenzie's "v" waves). It is this part of the venous pulse tracing which has been so little understood, and attention is called to the fact that in the present experiments the points of beginning and termination of the waves in question have been practically fixed in relation to the events in the cardiac cycle. Interpretation of these waves was, therefore, simple. Attention is also called to the conclusion that Bard's "intersystolic" wave is a normal phenomenon.

Methods of Experimentation

In the experiments to be reported dogs were used exclusively. Simultaneously with the pulsation in the superior vena cava the movements of the right auricle and right ventricle, the variations in intraventricular pressure, and the pulse from the innominate artery (or the subclavian, near its origin), were graphically recorded.

Ether was administered by means of intratracheal insufflation.

To obtain records of the venous and arterial pulsations a special form of receiving tambour was used. This consisted of a metal T-tube, the horizontal limb of which had been cut in half, lengthwise, and a thin rubber membrane loosely stretched across the half attached to the upright limb and made air-tight with rubber cement. The two halves were placed around the superior vena cava, as close as possible to the auricle, and the upright limb of the instrument was connected by small rubber tubing to a sensitive Marey recording tambour.

The auricular and ventricular myograms were recorded with a Cushny double spring myocardiograph, and the intraventricular pressure curves obtained by means of ordinary heart sounds passed through the innominate or subclavian arteries into the left ventricle and connected with a Marey recording tambour.

In the interpretation of the tracings every precaution was taken to guard against errors due to time consumed in propagation of pulse waves from the heart to the receiving tambours, or to delay in transmission to the recording tambours.

Tracings were obtained from hearts in pathological conditions (auricular fibrillation, heart block, etc.), as well as from normal hearts, and at times the movements of the a-v septum and ventricular volume curves (Henderson, '06.) were recorded.

Discussion of the Results of the Experiments

The Auricular or Presystolic Wave.[1] — Among recent investigators there has been unanimity of opinion concerning the time of occurrence and the direct cause of the auricular or pre-

[1] Mackenzie's "a" wave; Porter's "systolic rise" and "first diastolic fall."

systolic wave in the venous pulse curve. It is generally stated that it begins with, and is the result of, auricular systole.

In all of the present experiments this was found to be true. The upstroke of the "a" or "p" wave occurs simultaneously with the beginning of auricular systole and lasts normally for a period of from .05 to .07 second.

Now it has been generally accepted, and at times definitely stated (Cushny and Grosh, '07; Mackenzie, '02), that the rise and fall of the "a" wave corresponds to the systole and relaxation of the auricle. It is well established that the duration of a normal auricular systole is about .1 second and that the normal a-v (Mackenzie's a-c) interval is also equal to about .1 second. If these figures are accepted, the fallacy of the statement that the rise of the "a" wave continues throughout auricular systole is apparent. Were this statement correct, the upstroke of the "a" wave would continue throughout auricular contraction, i.e., for .1 second; then, as the a-v interval is also only .1 second, it would be prolonged into the systolic rise (Mackenzie's "c" wave), which occurs synchronous with the beginning of ventricular systole. In other words, there would be no downward stroke of the "a" wave.

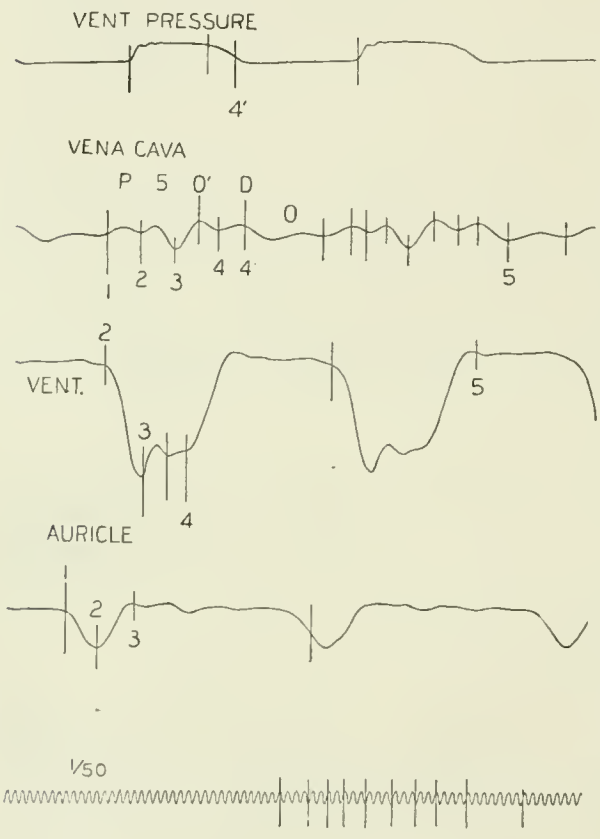


FIGURE 1. (One half the original size.) Normal. The second onflow wave shows well.

But such is not the case. In all of the tracings to be presented, both the rise and fall of the "a" wave have been completed by the end of auricular systole, the upstroke continuing, as has been stated, for .05 to .07 second and the downstroke having the same or a slightly longer duration. The presystolic fall is then terminated by the rise occurring coincident with ventricular systole.

Auricular myograms usually show the systolic movement of the recording lever rounding off slightly and passing directly into diastole, but in a number of the present tracings with a rapid drum a distinct plateau, or pause, is seen occurring between actual shortening and relaxation of the auricular musculature (Figs. 2, 3). This plateau is necessarily of very short duration, and when it does not appear in the tracing, it is probably due to the fact that it is entirely obscured by the fling of the recording lever.

The crest of the "a" wave coincides with the beginning of the auricular plateau, — that is, the upstroke of the "a" wave continues throughout the period of actual shortening of the auricular musculature. Then comes the fall of the "a" wave, which terminates with the end of the auricular plateau, or beginning of actual relaxation. At this point, or just before, also occurs ventricular systole and the systolic rise in the venous pulse.

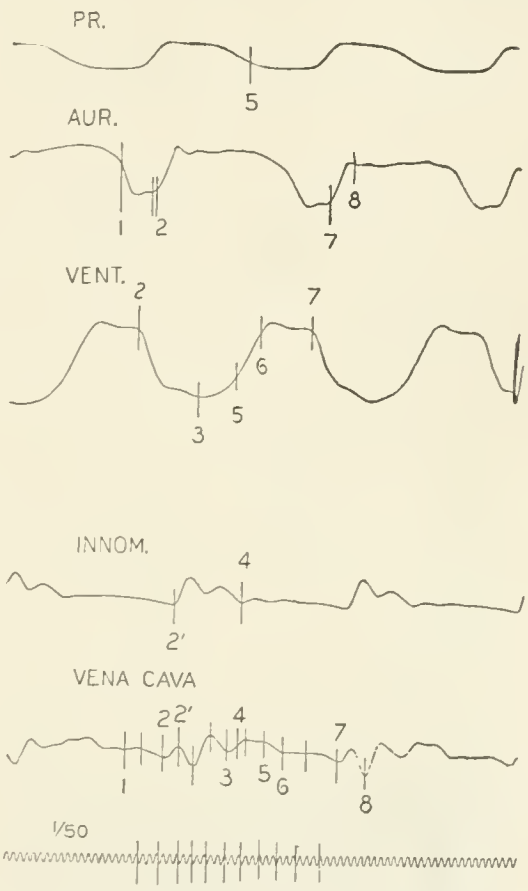


FIGURE 2. (One half the original size.) The plateau on the auricular myogram corresponds to the "pf." Because of slow ventricular relaxation the "d" wave is plateaued.

The manner in which the contraction of the auricle produces the presystolic wave is not exactly clear. There are three possibilities: (1) the wave may be due to actual regurgitation from the auricle into the great veins; (2) to stasis in the veins as the result of auricular systole; or (3) it may be a centrifugal wave of pressure transmitted through the veins as a result of impact from the auricle against the column of blood in the vena cava.

From the work of Keith, François-Franck, and Burton-Opitz it is probable that in case of normal hearts with good tone the presystolic rise in pressure is the result of stasis plus the

effect of impact from the auricle, actual reflux playing but little part.

The Intersystolic or Second Auricular Wave. — In man a second auricular wave has been observed by Piersol ('08), in a case of heart block and at times when only the auricle was beating. Piersol, however, made no attempt to explain the cause of the double "a" wave, although it was obviously of auricular origin.

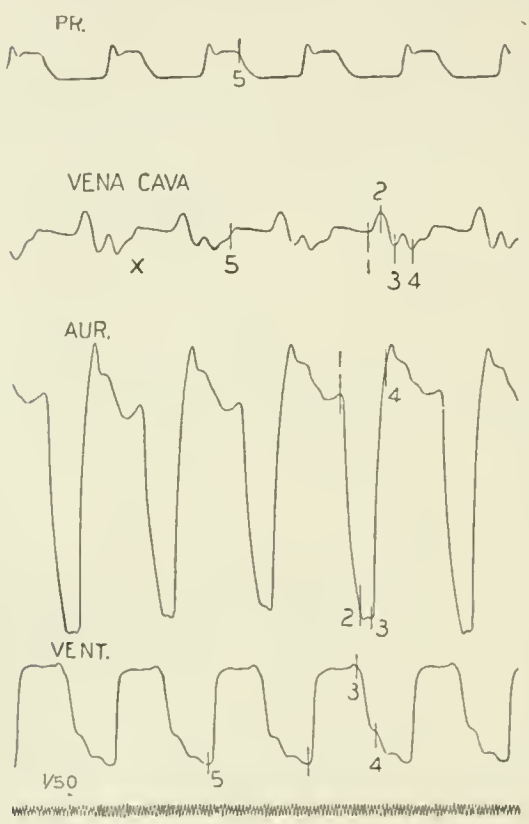


FIGURE 3. (One half the original size.) This tracing illustrates at "x" the writer's idea of the position of the first onflow wave relative to the "d" wave in the diastolic rise. The time relations of the "p" wave and the auricular myogram are well shown.

In the tracings to be presented, this second positive auricular wave may frequently be seen. It is shown especially well when the ventricle has been inhibited by vagus stimulation (Fig. 4) by fibrillation, or when the auricle contracts alone in cases of heart block produced by clamping the a-v bundle. (Figs. 5, 6.) In these tracings the upstroke of the second auricular wave begins upon the presystolic fall at precisely the same point at which the normal systolic rise would occur, had the ventricle been contracting. It also has practically the same duration as the systolic rise, from .04 to .06 second, and the time consumed by its downstroke is approximately equal to that of the normal systolic fall or auricular collapse, from .04 to .06 second. In other words, so well does the second auricular wave correspond to the normal systolic wave, that although only the auricle is contracting, it seems that the normal first and second positive and negative waves are still present, the latter, however, not being so pronounced. In relation to the auricular myogram, the second auricular wave occurs at the very beginning of the

relaxation, and the end of its downstroke comes at the point where full relaxation has been completed. (Figs. 5, 6.)

The second auricular wave is best shown when the auricle is contracting strongly and when the ventricle is not so engorged with blood that the auricle can not readily empty itself. In fact, it practically disappears when the auricle is weak and the heart is distended with blood. In Fig. 5 the second auricular wave is, at first, of good amplitude, but as the heart becomes more distended and the auricular contractions less strong, the wave is seen to diminish greatly in size.

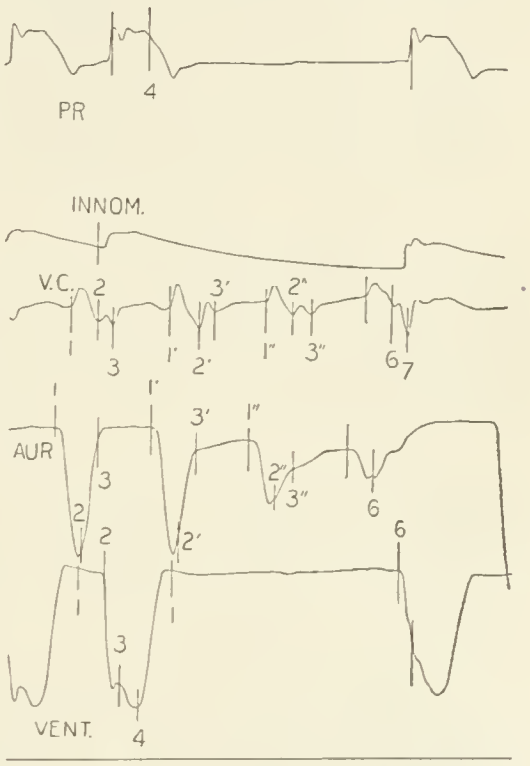


FIGURE 4. (One half the original size.) The ventricle has been slowed by stimulation of the vagus, without affecting the auricle very much. The second auricular wave 2″–3″ is seen to have the same time relations as the normal "s" wave. The independence of the first onflow wave of ventricular action is shown at 3″, where, with the ventricle inactive, the wave is practically normal.

Now it has been previously stated that the second auricular wave is the more pronounced the stronger the auricular contraction and the more completely the auricle can empty itself into the ventricle. It is probably due, therefore, to the recoil of a suddenly distended elastic ventricle, together with a further pushing up of the a-v valves by the blood which, as a result of auricular systole, has suddenly entered the ventricle and produced eddy currents behind the cusps of the valves. This rebound is readily understood if it is remembered that auricular systole finds the a-v valves practically closed by a well distended ventricle (Hill, '00; Gibson, '07; Hirschfelder, '07). The valves are forced open by the auricular systole and as soon as the contraction comes to an end, they will suddenly resume their former position. It is at this instant that the upstroke of the second auricular wave begins.

That there may actually be a rebound of the ventricle, after a

strong auricular systole, was indicated in one experiment. At one point upon the tracing the ventricle failed to respond to the auricular impulse, and the second auricular wave appeared. The ventricular volume tracing showed the normal increase during the first auricular wave, but there was a decrease in volume synchronous with the occurrence of the second auricular wave. This decrease in ventricular volume could only have been the result of an elastic rebound or of an actual reflux of blood into the auricle; and a reflux towards the auricle could have but one effect, viz., a rise in the venous pressure tracing.

This rise in pressure can continue, however, but for a short time, as the auricular cavity is now rapidly enlarging, due to relaxation. The increase in pressure is, therefore, soon terminated by a fall, which continues until the auricle is fully relaxed and filled by the flow of blood from the periphery.

Chauveau ('00) and Pachon ('09) studied the "intersystolic" period and demonstrated a small rise of intraventricular pressure occurring after the auricular and before the ventricular systole. This, they both concluded, was due to a slight increase in the tension of the papillary muscles, which then exerted a pull upon the a-v valves.

That the origin of the second auricular wave is entirely independent of the action of the papillary muscles is conclusively shown in the present experiments, since the wave occurs when the ventricle is not contracting.

In cases of very long a-v intervals in the jugular pulse of man, Bard ('06) has observed the appearance of a small wave between the auricular and ventricular systoles. He called it the "intersystolic" wave and assumed, without further evidence, that it was due to a recoil from the ventricle after auricular systole. In the present experiments this wave may also be seen in cases of long a-v intervals, and it is very probable that the intersystolic wave is identical with the second auricular wave. With normal a-v intervals, the second auricular wave is fused with the systolic wave, as the time relations of the two variations in pressure are the same. But if the ventricular systole is delayed, then the systolic rise does not come until so late that there is time for the second auricular wave to appear as a separate event, viz., the intersystolic wave.

This also explains why, at times, the systolic wave is doubly peaked, the systolic rise coming in such cases just after the termination of the second positive auricular wave.

From the present experiments it may be concluded, therefore, that the second auricular wave is a normal phenomenon, coinciding with the systolic wave or appearing as the intersystolic wave according to the length of the a-v interval.

The Systolic Rise.[1] — The systolic rise in the venous pulse tracing occurs synchronous with the beginning of ventricular systole, as indicated by the ventricular myogram and the intraventricular pressure curve.[2]

When compared with the auricular myogram, the tracings show that the systolic rise appears just at the beginning of actual relaxation. This must necessarily vary, of course, with the length of the a-v interval, so that with long a-v intervals the systolic rise would occur sometime after the auricular relaxation had begun.

The duration of the systolic rise in the venous pulse is usually from .04 to .06 second, that is, the increase in pressure continues practically throughout the presphygmic period of the ventricle. The opening of the semilunar valves, as indicated by the appearance of the pulse in the innominate artery, occurs just before the termination of the systolic rise. These same time relations for the systolic rise have also been obtained by Porter, Fredericq, Morrow, Hirschfelder, Bard, and others.

Mackenzie and Wenckebach, however, believe the wave to be synchronous with the carotid pulsation in the neck. Nor do they recognize the occurrence of the wave in the intra-auricular pressure curve, but hold that it is due entirely to impact of the

[1] Mackenzie's "c" wave; Porter's first diastolic rise; Morrow's systolic or ventricular wave.

[2] To determine this point, .01 to .02 second must sometimes be allowed for propagation of the wave from the heart to the receiving tambour, using as a basis for calculation Morrow's ('00) results showing that the venous pulse waves travel at a rate of 1 to 3 metres per second. In many animals, however, when the blood in the vena cava was at a high tension, it was not necessary to allow even this small fraction of a second for delay, as the systolic rise and the beginning of ventricular systole occurred exactly simultaneously.

carotid artery against the jugular, from which vein the tracing is usually taken in man.

Now, in the present experiments from a series of over fifty animals this wave has never failed to appear in the pulse tracings taken from the superior vena cava, two or three centimetres above the auricle. The wave, under these conditions, appearing in the vena cava before the pulse of the carotid, could not possibly be the result of impact from that artery. Bard ('06) has shown, moreover, that even in the neck the systolic rise appears before the carotid pulsation, and Morrow ('06), after eliminating all possibility of arterial impact by clamping the carotid near the aorta, found that the wave still appeared in the jugular pulse tracing.

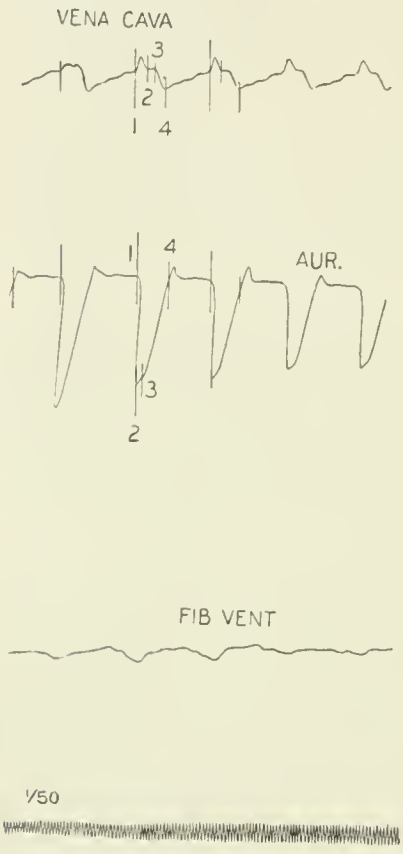


FIGURE 5. (One half the original size.) The ventricle has just begun to fibrillate. The "p," second auricular, and first onflow waves are present. The auricular collapse, 3–4, is of normal depth, although the ventricle is inactive. Compare this pulse tracing with 7*d*, where only the ventricle is contracting.

From the above it may be seen that although the carotid pulsation may augment the systolic rise in the jugular pulse, it cannot be the primary cause in the production of the wave. There is still to be considered, however, the possibility of the wave being produced by impact of the aorta against the auricle and vena cava, as was suggested by Friedreich ('65) and Potain ('67).

To determine this point, in the experiments to be reported, when only the ventricle was contracting, the aorta and its branches were, with a retractor, held two centimetres away from the right auricle and vena cava. It is necessary that the auricular contraction be eliminated in such an experiment, in order that the second auricular wave will not be confused with the systolic rise. Under the above conditions a rise in the venous pulse tracing still occurred synchronous with the beginning of ventricular systole, thus proving that the

wave originated within the heart itself as a result of the ventricular contraction. Also, Fredericq ('07) has pointed out that, as the systolic rise is approximately synchronous with the carotid pulsation in the neck, the wave could not be the result of aortic impact on account of the different rates of propagation of the venous and arterial pulse waves.

In the present tracings, in cases of extra systoles or heart block, when the ventricle contracted independently of the auricle, the systolic rise may always be seen occurring synchronous with the commencement of ventricular systole, just as in the normal cardiac cycle (Fig. 7*d*). From the above it is evident that the cause of the systolic rise is connected with the contraction of the ventricle. All investigators who have recognized the rise as occurring in the intra-auricular pressure curve (Porter, '92, in both right and left auricles; Morrow, '07; Hirschfelder, '10; Fredericq, '07; and others) have attributed it to an upward movement of the a-v valvular diaphragm, as a result of the increased pressure within the ventricle during the presphygmic period; and Morrow ('07) recognized, as additional causative factors, the contraction of the ring of muscle in the a-v junction and the possible pressure exerted upon the auricles by the systolic twist of the heart.

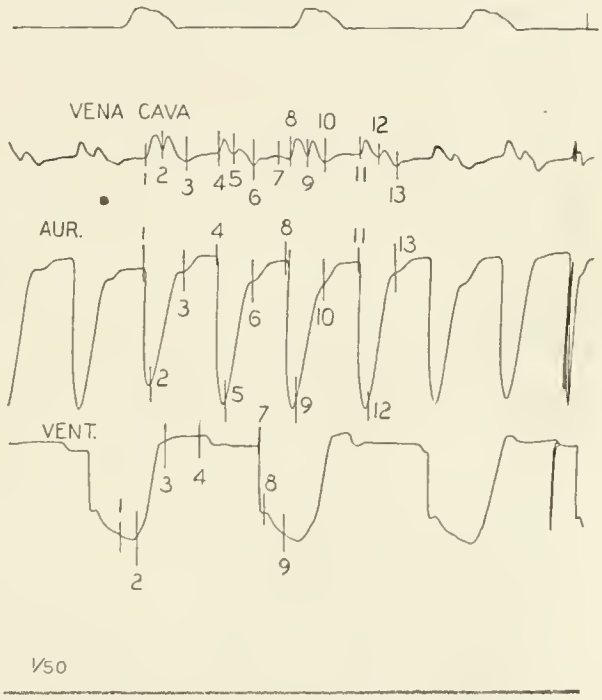


FIGURE 6. (One half the original size.) Heart block; 2–3, the second auricular and "d" waves are fused. 5–6, the second auricular wave. 6, the first onflow wave.

Gerhardt ('94) believed that during ventricular systole the a-v ring is so constricted that the valves could not be forced up enough to convey the ventricular impact, but Chauveau and Faivre ('56), after the insertion of a finger into the auricle of a living heart, reported that the a-v orifice was not completely

closed during ventricular systole, as the convex valvular diaphragm was palpable at this time. That an upward movement of the a-v diaphragm is possible at the beginning of systole was also indicated by the results of Roy and Adami ('90) which showed that the pull upon the valves by the papillary muscles comes after the contraction of the wall of the ventricle.

Haycraft and Paterson ('96), however, disputed this statement, and held that the papillary muscles and the rest of the ventricle contract simultaneously, while Saltzman ('08) has recently supported Roy and Adami with the conclusion that the papillary muscles contract on an average of .03 second after the base of the ventricle. At any rate, whether the papillary muscles contract after the base of the ventricle or not, Roy and Adami's tracings show a delayed downward movement of the a-v valvular diaphragm, which might be the result of either delayed contraction of the papillary muscles or the inability of those muscles to pull down the valves against the ventricular contents until the semilunar valves have opened. This is an important point, for if the a-v diaphragm moved downward at the very beginning of ventricular systole, the auricular cavity would be enlarged, so that the effect of the impact would be lost in the then existing low auricular pressure.

It seems reasonable to assume, therefore, that the systolic rise is the result of a slight bulging upward of the a-v valves and of the impact from the suddenly contracting ventricle, through the valves, against the auricular contents.

Concerning the cause of termination of the systolic rise, there are two possible explanations:

First, Reference to the tracings will show that the auricle is rapidly relaxing at this point, and the increased size of the auricular cavity forms a sufficient explanation of the disappearance of the slight positive wave of pressure produced either by impact or the ballooning up of the a-v diaphragm.

Second, Roy and Adami's tracings show that the downward movement of the a-v valvular diaphragm begins about at the end of the presphygmic period, that is, just before the end of the systolic rise in the venous pulse tracing. Just as the upward movement of the a-v diaphragm might produce the systolic

rise, would not the downward movement terminate the increased pressure?

The Systolic Fall or Auricular Collapse.[1] — The systolic fall, or auricular collapse, in the venous pulse tracing begins with the end of the systolic rise, just after the opening of the semilunar valves. Upon the auricular myogram it is seen that the beginning of the systolic fall usually occurs from .03 to .05 second after actual relaxation has set in, and continues until the end of complete relaxation of the auricle. The systolic fall represents the greatest decrease in auricular pressure that occurs during the cardiac cycle and has been given a value of − 10 mm. Hg by Porter ('92). This fall of intra-auricular pressure is of the greatest importance in the filling of the heart, for Burton-Opitz has shown that it is during this period that the most marked acceleration of the blood flow occurs in the veins of the neck.

The present results support the statements made by Porter ('92), Fredericq ('07), Hirschfelder ('07), and others concerning the time of commencement of the systolic fall, but they do not agree with most of the previous reports as to the point of termination of this decrease in pressure. Most authors (Gottwalt, '81; Mackenzie, '08; Hering, '04; Morrow, '07) recognized the end of the systolic fall as occurring during systole of the ventricle and usually place it just before the beginning of its relaxation. Porter ('92) states that the fall is terminated "near the beginning of ventricular relaxation," but in his Figs. 22 and 23 it is undoubtedly brought to a close during the first half of systole, synchronous with the superposed wave at the beginning of the plateau of the intraventricular pressure curve. In his Figs. 13 and 14 the end of the fall occurs at the middle of the ventricular plateau. In his diagram, Fredericq ('07) has placed the end of the systolic fall well into the first half of the ventricular plateau, but in his description he speaks of the negative wave "cd" as passing into the positive wave "def," the notches of which represent different stages of relaxation of the ventricle; consequently the relations of this part of his venous pulse curve can not definitely be understood.

[1] Mackenzie's "x′" fall; Porter's second diastolic fall; Bard's "RO"; Gerhardt's systolic collapse.

Other investigators (Gerhardt, '94; Wenckebach, '06) hold that the end of the systolic fall, or beginning of the third positive wave, is synchronous with the beginning of ventricular relaxation.

In the tracings to be presented, the termination of the systolic fall, coming as it does invariably just after the superposed wave at the beginning of the ventricular myogram or pressure curve (as in Porter's Figs. 22 and 23), is one of the most constant points in the venous pulse curve and, as has been stated, is always synchronous with the end of auricular relaxation. The fall has a

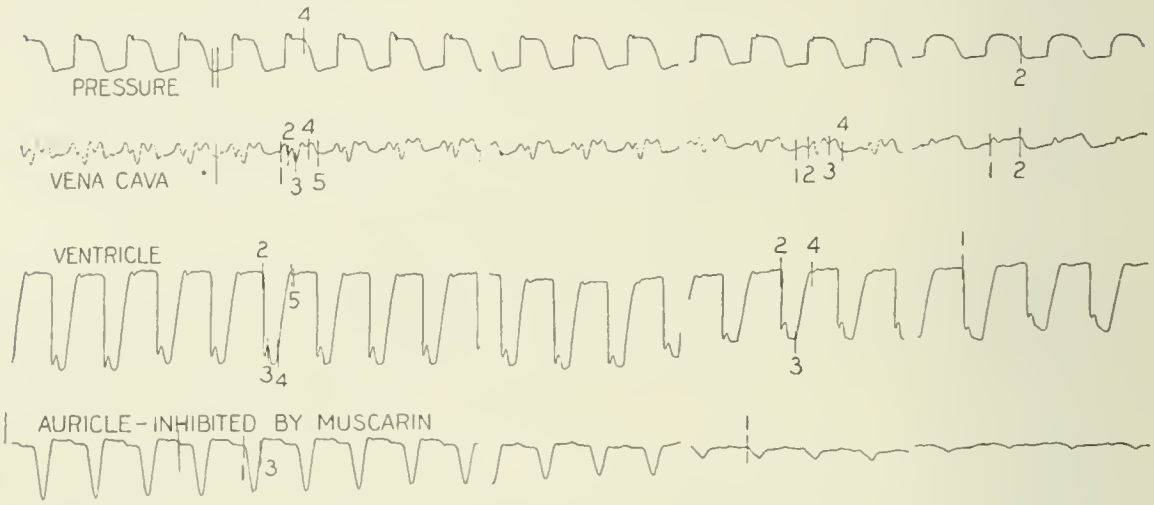


FIGURE 7*a*, *b*, *c*, *d*. (One half the original size.) These tracings show the changes in the phlebogram as the auricle passes into a state of inhibition following an injection of muscarin. Note the change in the relative positions of the "p" and "s" waves (a–v interval constant). The dependence of the "ac" upon the activity of the auricle is demonstrated by the fact that its depth varies directly with the amplitude of the auricular systoles. The second onflow and sinus ("w") waves appear (7*a*). The depth of the "df" in 7*d*, with the auricle inactive, is normal.

duration of from .04 to .06 second, which places its termination, therefore, about at the end of the first third of ventricular systole.

The majority of investigators believe that the systolic fall in pressure in the veins is due to the enlargement of the auricular cavity, thus producing a sudden inrush of blood after the stasis caused by the auricular systole. This enlargement of the auricle has been supposed by Fredericq ('07) to be largely the result of the downward movement of the a-v valvular diaphragm with ventricular systole. Wenckebach ('06) and Morrow ('07) showed,

however, that the systolic fall was still present, though reduced in size, when the ventricle was not contracting.

In the experiments to be reported, it was found that elimination of the auricular contractions by stimulation of the vagus, injection of muscarin, or fibrillation abolished the auricular collapse in the venous pulse almost completely (Figs. 7*a*, *b*, *c*, *d*). In such cases the venous pulse resembles a reversed sphygmogram broken by the normal systolic rise and a slight systolic fall. On the other hand, if the contractions of the ventricle were eliminated by fibrillation, stimulation of the vagus, or clamping the a-v bundle, the systolic fall reached almost its normal depth (Fig. 5).

In view of the fact that in the present tracings, with only the auricle contracting, the decrease in pressure is at least twice what it is with only the ventricle beating, it can only be concluded that the auricular relaxation is the predominating factor in the production of the negative wave. If the downward movement of the a-v septum, as well as that of the valvular diaphragm, were a primary factor in producing the systolic fall, then the depression should continue until later in systole. This, however, is not the case.

As the auricular cavity ceases to enlarge, the rapid onflow of blood from the periphery must fill the veins, and the fall in pressure is changed to a positive wave. That the cause of the termination of the decrease in pressure can not be referred to any action of the ventricle as a whole is indicated by the fact that the base of the ventricle is still moving downward at this time (present tracings).

In conclusion it may be said that, since the systolic fall, or auricular collapse, is never so great when any part of the heart beat is eliminated as in the normal cardiac cycle, both the auricular relaxation and the downward movement of the a-v diaphragm must be recognized as causative factors in the production of the decrease in pressure. The effect of the former, however, predominates.

The First Onflow or Prediastolic Wave.[1] — Most authors

[1] Bard's telesystolic wave; the first part of Mackenzie's "v" wave; Porter's second diastolic rise (first part); Gerhardts' first diastolic wave (first part.)

have recognized but one positive wave, in the venous pulse curve, occurring after the auricular collapse; this rise in pressure, the third positive wave, corresponds in general to Mackenzie's "v" wave and, according to the various authors, occurs either during ventricular systole or at the beginning of diastole. Fredericq ('07) has concluded that the rise is notched at different points by the successive stages of ventricular relaxation, while Bard ('06) described the increase in pressure as consisting of two separate and distinct waves, — "telesystolic" and "protodiastolic." The "t" wave, Bard says, appears at the end of ventricular systole, and the "d" wave, then, occurs at the very beginning of diastole.

In the present tracings it has been found that the rise in pressure, following the auricular collapse, consists of at least two waves. The first will be called the "First Onflow Wave" (after Morrow, '07) and the second the "Diastolic Rise." The two waves will be discussed as separate phenomena.

The first onflow wave begins with the termination of the auricular collapse, or systolic fall, precisely at the end of the complete relaxation of the auricle. This point is determined by reference to the auricular myograms in all tracings. In relation to the movements of the ventricle it is found that the wave occurs during the first half of systole, synchronous with the superposed wave at the beginning of the plateau in the ventricular myogram. This would place it just about at the predicrotic notch on the sphygmogram from the innominate artery.

The pressure then rises sharply for a period of from .04 to .06 second, after which it may rise or fall slightly, or remain practically constant, taking the form of a short plateau. This second part of the first onflow wave also has a duration of from .04 to .06 second, but it is usually somewhat shorter than the first part. The termination of the entire first onflow wave is synchronous with the very beginning of relaxation of the ventricle before the closure of the semilunar valves. (All tracings.)

In explaining the origin of this wave, most authors have discussed it in connection with the diastolic rise following it. Porter ('92) believed that the rapid onflow of blood from the periphery, after auricular relaxation, was a factor in the production of his second diastolic rise, while Gottwalt ('81) and Morrow ('07)

recognized onflow as the most important cause of their third positive waves. In fact, Morrow has named the rise in pressure the "first onflow wave," but he believes that it appears at about the time of closure of the semilunar valves, whereas, in the experiments to be reported, it always begins in the first half of systole.

Gibson ('80) and Mackenzie ('07), while recognizing that onflow of blood from the periphery constitutes a contributory cause of the third positive wave ("v" wave), hold that tricuspid regurgitation normally plays an important part in producing the rise in pressure.

Undoubtedly, tricuspid regurgitation would produce just such a wave as the first onflow wave here described, but, even admitting that the valves are normally incompetent (which physiologists in general do not do), it would be impossible to assume that the regurgitation would occur at exactly the same time in every heart. Such a statement would be necessary, however, to explain the invariable appearance of the first onflow wave at a fixed point in the heart cycle, — viz., at the end of full relaxation of the auricle.

As previously stated, the wave can not be ascribed to the action of the ventricle at this point, since the a-v septum is still moving towards the apex and such a movement would produce a negative, rather than a positive, variation in pressure. Now, as the auricular cavity is enlarging, due mainly to relaxation (and partially to the downward movement of the a-v valvular diaphragm), it must be assumed that the venous blood is filling it almost as rapidly as its volume increases, so that the instant relaxation is completed, the blood, not being able to enter the auricle, must necessarily enlarge the veins and "back up" towards the periphery. The resulting rise in pressure is the first onflow wave.

As Morrow ('07) has pointed out, the first onflow wave is by no means dependent upon the action of the ventricle, for when the auricle only is beating, it is practically as pronounced as in the normal cardiac cycle. (Figs. 4, 6.) Furthermore, with the auricular contractions eliminated, the wave does not have nearly so great an amplitude as when only the auricle is contracting. (Tracing 7*a*, *b*, *c*, *d*.) This is additional evidence against possible

ventricular origin such as movements of the a-v septum or tricuspid regurgitation. Of course, the wave, with any part of the normal cycle eliminated, could not be so pronounced as when both auricle and ventricle contract. If the ventricle, because of its inhibition, does not empty itself, then the auricle will remain fairly well filled, even after a strong contraction, and consequently there can be but slight further onflow. And if only the ventricle contracts, then the auricle will remain even more distended than before and there will be less onflow. (Figs. 5, 7*d*.) Normally, the rise in pressure constituting the first onflow wave will continue until the vein is filled to its capacity and will then be continued as a sloping plateau until terminated by the diastolic rise, which occurs synchronously with the beginning of relaxation of the ventricle.

The Diastolic Rise and Fall.[1] — The diastolic rise in the present pulse curves terminates the first onflow wave precisely at the beginning of ventricular relaxation. The tracing at this point rises rather sharply for a period of .05 to .08 second, at times rounding off as a distinct plateau for .03 to .04 second, and is finally terminated by the diastolic fall. The entire positive wave has normally a duration of from .06 to .10 second.

The time of closure of the semilunar valves, obtained from the arterial sphygmogram, occurs about .01 to .02 second after the rise begins, a fact which would exclude the possibility of the wave being due to impact through the ventricle from the closure of the valves as suggested by Riegel ('82).

The termination of the diastolic rise occurs approximately with the opening of the a-v valves, as indicated by the intraventricular pressure curve.

In regard to the cause of the wave, as the auricle is distended and passive at the time of its occurrence, the origin of the increased pressure must be referred to some action of the ventricle. Since the ventricle is just beginning to relax as the rise in the venous pulse curve begins, it is reasonable to assume that the upward movement of the base of the ventricle pushes the column of blood in the auricle and vena cava before it, thus causing the

[1] Bard's protodiastolic wave; second part of Mackenzie's "v" wave and "y" fall; second part of Morrow's first onflow wave and ventricular collapse.

increase in pressure. That the base of the ventricle actually begins its upward movement just as the diastolic rise appears, has been shown by the method previously described.

Other authors (Porter, '92; Gerhardt, '02; Wenkebach, '06; Fredericq, '07), in discussing the third general rise in the venous pulse curve, have ascribed its cause to the return of the base of the ventricle, but they included in this positive wave the diastolic rise and the first onflow wave as well; the experiments to be reported, however, show them to be separate waves and with different origins.

The diastolic rise continues with the upward movement of the base of the ventricle until the intraventricular pressure is sufficiently low to allow the a-v valves to open. At this point the column of blood in the auricle and vena cava, which was being pushed up, rushes into the relaxing ventricle and the diastolic rise is terminated by the diastolic fall.

The form of the diastolic rise varies greatly according to whether the ventricle relaxes rapidly or slowly. In both cases the rise begins at the same point, but with a rapidly relaxing heart the postsphygmic period is so short that the wave is soon terminated by the opening of the a-v valves and the diastolic fall. But if the ventricle relaxes slowly, the time of opening of the valves is delayed, and consequently the diastolic rise is prolonged into the definite plateau previously described. Both types of the diastolic wave, as well as an intermediate stage, may be seen in Figs. 1 and 2. Examination of the ventricular myograms will show that if there is a plateau upon the wave, the relaxation of the ventricle is much more prolonged than in cases where the diastolic wave is a simple rise and fall.

To determine the above points definitely, the percentage parts of the complete cycle which were equal to the systole and actual relaxation of the ventricle were calculated in different experiments. It was found that the relative lengths of the systoles of hearts beating at different rates did not vary much, being usually from 35 per cent to 38 per cent of the cycle. The periods of relaxation did vary greatly, however, from 20 per cent to 32 per cent. In cases of rapid relaxation (20 per cent of the cycle) there was never any plateau upon the diastolic rise in the venous

pulse curve, but with hearts whose relaxation was 28 per cent to 32 per cent of the cycle the plateau was always present.

That the diastolic fall is primarily the result of the rush of blood into the ventricle at this time has been accepted by all investigators. The fall continues until the end of actual relaxation of the ventricle, a period of from .05 to .08 second, and is then terminated by the second onflow wave. This point is always synchronous with the end of relaxation as indicated by the ventricular myograms, and is also synchronous with the end of diastole and the beginning of diastasis in the ventricular volume curve. At this time, as the ventricle has filled simultaneously with its relaxation, the a-v valves are floated up and almost closed (Hill, '00), so that the onflow of blood "backs up" into the auricle and the veins, and the negative wave becomes positive.

With only the auricle beating, the diastolic rise and fall are absent (Figs. 4, 5). Morrow ('07) thought that, with the ventricle inhibited, his tracings still showed the third positive wave, but he undoubtedly confused the true diastolic rise with the rise in pressure corresponding to the present onflow wave. The latter wave is, as has been stated, always present when only the auricle is contracting. Under such conditions the present tracings resemble those of Morrow very closely.

When the ventricle only is contracting, however, the diastolic rise, and especially the diastolic fall, are practically unchanged from the normal. (Fig. 7*d*.) Just as the auricular collapse, or systolic fall, is dependent primarily upon the relaxation of the auricle, so is the diastolic fall dependent entirely upon the collapse of the ventricle. The terminations of the systolic fall and auricular relaxation are simultaneous, and, as has just been stated, the diastolic fall and ventricular relaxation come to an end synchronously.

Concerning the Variation in the Position of the First Onflow Wave in Relation to the Diastolic Rise. — From the literature it is evident that the greatest discrepancies exist between the reports of the different investigators concerning the onset of the third positive wave in the venous pulse.

In the tracings here presented, the first onflow wave in the

pulse from the vena cava begins invariably with the end of auricular relaxation and during the first half of ventricular systole. On the other hand, it seems equally true that the third positive wave (Mackenzie's "v" wave) in the jugular pulse of man occurs somewhat later in ventricular systole. It must be remembered, in this connection, that the third positive wave in the jugular pulse exists as a fusion of the first onflow wave and the diastolic rise of the present tracings. (Such a fusion is shown in Fig. 3.)

The familiar notch upon Mackenzie's ('02) (Fig. 210) "v" wave, occurring just before the arterial dicrotic notch, undoubtedly marks the termination of the first onflow wave and the beginning of the diastolic rise. In such a tracing it is evident that the first onflow wave did not appear until later in systole than it does in the present tracings.

Now Morrow ('00) has shown that the first onflow wave travels at a slower rate than the other waves of the venous pulse. Such a conclusion is reasonable in view of the different origins of the various waves. The "p," "s," and "d" waves are essentially impact waves, whereas the first onflow wave is dependent for its rate of propagation upon the rapidity of the onflow of blood from the periphery. The impact waves of the pulse leave the heart in the order "p" "s," "d." At the end of the auricular collapse the onflow wave will appear instantaneously in the sino-auricular region and consequently must occur well before the diastolic rise has originated. As the veins fill, the wave will appear next in the upper vena cava and finally in the veins of the neck.

In the meantime the diastolic rise, which, as an impact wave, must have a more rapid rate of propagation than one dependent upon the rapidity with which the veins fill, has originated in the auricle and reached the neck almost simultaneously with the first onflow wave.

That this is the true explanation of the early appearance of the first onflow wave in the vena cava and its late appearance in the jugular has been shown experimentally. In this experiment the venous pulse was obtained from the external jugular in the neck, and then, in the same animal, the pulse of the vena cava was recorded. It was found in the latter case that although the heart rate had slowed somewhat, the period from the termination

of the systolic rise to the beginning of the first onflow wave had diminished in time, the actual figures being as follows:

Jugular Pulse: (Cycle .42 sec.).

From crest of "s" to "o" = .10 sec., or 23 per cent of the cycle.

Vena Cava Pulse: (Cycle. 52 sec.).

From crest of "s" to "o" = .05 sec., or 9 per cent of the cycle.

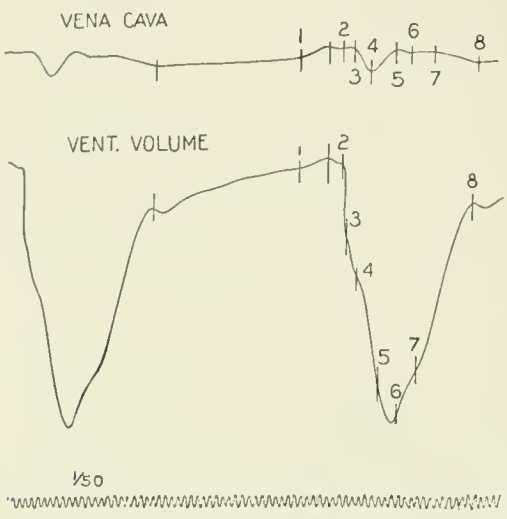


FIGURE 8. (One half the original size.) Showing the relation of the phlebogram to the ventricular volume curve. Note that at 8 the diastolic fall ends with the beginning of the period of diastasis on the volume curve.

In other words, the first onflow wave appears in the venous pulse cycle just .05 second later in the jugular than in the vena cava.

That this difference in relative position was actually due to a relative delay in the appearance of the onflow wave, and not to a prolongation of the auricular collapse, was shown by the tracing from the jugular, on which, in many cases, it was seen that the auricular collapse had definitely ended and was followed by a rounded off interval, during which no further fall occurred before the appearance of the first onflow wave.

The general spatial relationship of the various waves at different regions may be expressed as follows, the waves leaving the heart in the order "p," "s," "o," "d":

Lower Vena Cava		*Upper Vena Cava*		*Jugular*
"d" "s" "p"		"d" "s" "p"		"d" "s" "p"
"o"	——>	"o"	——>	"o"

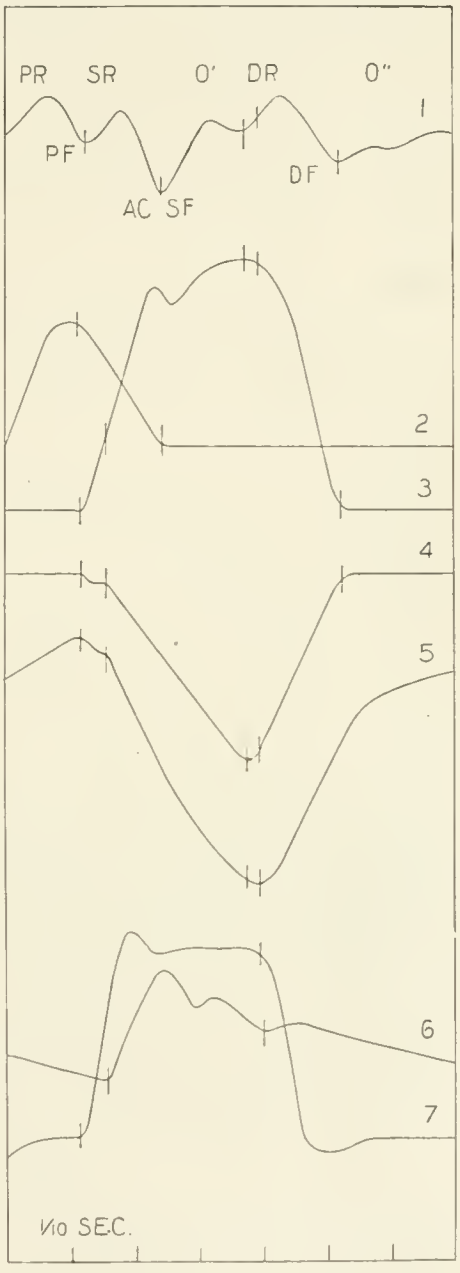
They would appear upon the tracing:

"p" "s" "d"	"p" "s" "d"	"p" "s" "d"
"o"	"o"	"o"

From the above it is seen that the position of the diastolic wave does not change, but that the relative position of the first

onflow wave will vary directly with the point from which the tracing is obtained and with the rapidity of the onflow.

It is evident that the discrepancies in the reports concerning the beginning of the third general rise in the venous pulse are due to the fact that the majority of investigators have considered the appearance of the onflow wave as the beginning of the diastolic rise, and under such circumstances their third positive waves (Mackenzie's "v" wave) would, of course, be reported as occurring in different positions, changing with the distance from the heart and the rapidity of the onflow.



The Second Onflow Wave. — After the opening of the a-v valves the onflow into the ventricle is not quite equal to the degree of relaxation and the diastolic fall in pressure occurs. Then, as the enlargement of the ventricular cavity reaches its maximum, the onflow volume can no longer be taken care of, and the increase in pressure, as the second onflow wave, will appear in the auricle and veins.

The beginning of this wave is synchronous with the end of complete relaxation of the ventricle, that is, just at the point when further enlargement of the ventricle

FIGURE 9. Diagrammatic representation of the events in the cardiac cycle, in relation to the normal pulse tracing from the superior vena cava. (1) Curve from the vena cava, showing the following variations in pressure: — presystolic rise and fall, systolic rise and fall; first onflow wave, diastolic rise and fall, and the second onflow wave; (2) auricular myogram; (3) ventricular myogram; (4) record of the movements of the a-v septum; (5) ventricular volume curve; (6) aortic pressure; (7) intraventricular pressure curve.

ceases and consequently stops the rapid inflow from the auricle and veins. This is also indicated by the ventricular volume curves, which show that the inflow of blood is practically completed as the second onflow wave appears, since it is at this point that the period of diastasis begins.

Hirschfelder ('07) and Gibson ('07) independently described this wave (Hirschfelder's "h" and Gibson's "b" wave), and both attributed it to the same cause, viz., the closure of the a-v valves at the beginning of the period of diastasis in the volume curve. Gibson reported, also, that a slight sound occurred at the same time.

It is doubtful, however, whether the a-v valves actually close at this time, for there is still a steady, though gradual, increase in the volume of the ventricle. It is generally accepted that the valves are floated up by the inrushing blood, so that when the ventricle is completely filled, the valves are in a position "ready for closure" (Hill, '00). It is hardly probable that this movement occurs with sufficient speed and force to produce a true impact wave, so that the movement of the valves is a secondary factor. As the blood reaches the distended ventricle and partially closed valves, it must "back up" into the auricle and veins, and because of the suddenness of the termination of the greater part of the onflow the stasis takes the form of a small wave. It is exactly analogous to the first onflow wave which appears at the end of the auricular relaxation, and for a similar reason.

There is slight difference between Gibson's hypothesis and the present one. In this paper the wave is regarded as a pure onflow wave, whereas Gibson and Hirschfelder ascribe it to the closure of the valves resulting from onflow.

The second onflow wave, in most of the present tracings, has a duration of .08 to .14 second and is usually followed immediately by the next presystolic or auricular wave. (Fig. 1.) In rapidly beating hearts the auricular systole follows closely upon the ventricular relaxation (diastolic fall) and consequently the second onflow wave does not appear.

A small wave, "w," occurring between the second onflow and auricular waves, has been described by Hirschfelder ('10), who assumed that possibly it was caused by the contraction of the

remaining embryonic tissue at the mouth of the vena cava, which would occur just before the auricular systole. This wave is also shown in some of the present tracings (7*a*).

It must be remembered that both the second onflow wave and Hirschfelder's "sinus wave" are simply superposed upon the general rise in pressure which, as the result of steady onflow from

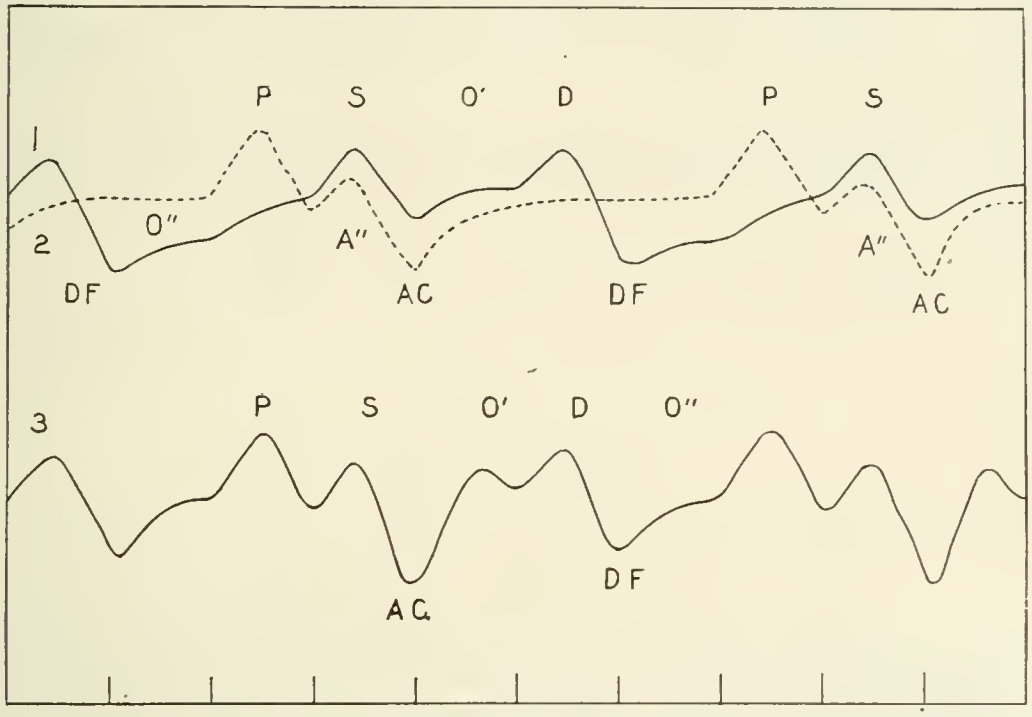


FIGURE 10. Comparison of a purely auricular pulse tracing (2) and a purely ventricular tracing (1). With only the auricule contracting, the normal auricular, second auricular, and first onflow waves, and a marked auricular collapse ("ac") are shown. When only the ventricule is beating, the systolic, diastolic, and small second onflow waves are present. The "ac" is but slight, whereas the "df" is normal. By combining the two curves, (1) and (2), a normal pulse tracing (3), would be obtained.

the periphery, continues throughout the common pause of auricle and ventricle.

GENERAL DISCUSSION

From the data presented in previous pages, it may be seen that the venous pulse in the dog is a normal phenomenon which consists of at least four waves — "p," "s," "o," "d" — separate both in time and in origin. In addition the second auricular, or intersystolic wave, may appear during a long a-v interval, and in cases of long periods of diastasis the second onflow wave is always seen.

In deciding upon the names for the various waves, it is imperative that the terminology used in most clinical textbooks (Mackenzie's "a," "c," "v," "x," and "y" waves) be changed, for the reason that such names do not describe sufficiently the times of occurrence or the causes of the different variations in pressure. Furthermore, it has been shown that Mackenzie's "c" wave, so named because he supposed that it was due to impact from the carotid artery, has nothing whatever to do with that phenomenon.

With slight changes, the nomenclature given by Morrow ('07) has been selected, since in most cases the terms indicate both the

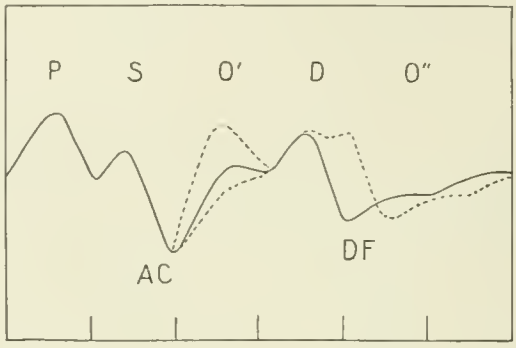


FIGURE 11. The form of the first onflow wave would probably vary with the rapidity of the onflow of blood from the periphery; the slower the flow, the less marked will be the wave (dotted lines). The change from the normal to the "plateaued" "d" wave, in case of slow relaxation of the ventricle and consequent late opening of the a-v valves, is shown by the dotted line in the last part of the figure.

time relations and modes of origin of the different waves. Morrow, however, applied the term "first onflow" to the combined rise in pressure consisting of the true first onflow wave and diastolic rise; and since these two waves are separate both in time and origin, it became necessary to give them different names. Morrow also suggested that the second onflow waves might be called "diastolic waves." The objection to this is that it would cause confusion between the onflow waves, which appear during diastasis, and the rise and fall which occur during the real diastole (Henderson, '06) of the ventricle.

Attention is called to the general similarity of the form of the venous pulse with only the auricle and the form when only the ventricle is contracting (Figs. 10, 5, 7*d*). Both resemble reversed

sphygmograms with the first and second auricular waves in the former case, and the systolic wave in the latter, superposed upon the general rise in pressure which is due to the continual onflow of blood from the periphery. When only the auricle is beating, the large fall in pressure comes with auricular relaxation and is then followed by a general rise due to onflow. With only the ventricle contracting, the greatest fall is during collapse of the ventricle and is followed by a general rise in pressure, also due to onflow from the periphery.

By this comparison of the two forms of the pulse it is demonstrated more conclusively than ever that the presystolic rise and fall, the intersystolic wave, and the systolic fall are dependent upon the movements of the auricle and, in like manner, the systolic rise and diastolic rise and fall are caused by the action of the ventricle.

Conclusions

The venous pulse in the dog is a normal phenomenon and consists of the following waves:

1. Presystolic rise, or auricular wave, corresponding to and caused by the actual shortening of the auricular musculature. It is essentially an impact wave, added to the increased pressure resulting from stasis in the large veins at this time.

2. The presystolic fall, occupying the slight pause between the end of contraction and the *beginning* of actual relaxation of the auricular musculature; it is due to the resumption of blood flow towards the heart and to the natural termination of the effect of the impact shock which caused the presystolic rise.

3. The intersystolic, or second auricular wave. This wave normally coincides with and augments the "s" wave, but appears between the "p" and "s" waves in cases of long a-v intervals. It follows the "p" wave when the auricle is beating alone. The intersystolic wave is the result of a recoil from the ventricle, following a strong auricular contraction.

4. The systolic rise, occurring synchronously with the beginning of ventricular systole; it is caused by the sudden closure and ballooning up of the a-v valves.

5. The systolic fall, or auricular collapse, beginning just after the opening of the semilunar valves and ending with the completion of auricular relaxation. The systolic fall is due to the enlargement of the auricular cavity, resulting principally from relaxation of the auricle itself and only very slightly from the downward movement of the a-v valvular diaphragm.

6. The first onflow or prediastolic wave, lasting from the end of auricular relaxation until the commencement of ventricular diastole; it is due to the rapid onflow of blood from the periphery.

7. The diastolic rise, from the beginning of ventricular relaxation to or slightly beyond the opening of the a-v valves; it is caused by the upward movement of the a-v septum.

8. The diastolic fall, from the opening of the a-v valves until the beginning of the period of diastasis; it is the result of the rush of blood from the auricle and great veins into the ventricle.

9. The second onflow wave, occurring at the end of rapid filling of the ventricle; it is due, therefore, to the beginning of stasis in the auricle and veins. The second onflow wave is analogous to the first onflow wave in mode or origin.

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THE INFLUENCE OF CAFFEIN ON THE ELIMINATION OF CREATINE AND CREATININE

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INVESTIGATIONS to determine the source of creatine and creatinine in the body also led to numerous inquiries concerning the rôle which the nervous system and the muscles play in the metabolism of these substances. The observations were made under various conditions of health and disease, including different degrees of muscular and nervous activity. The results obtained by Van Hoogenhuyze and Verploegh,[1] Lefman,[2] Shaffer,[3] Brown and Cathcart,[4] and Melanby[5] indicate that in man and the lower animals muscular activity is without effect. Evidence, however, is not wanting that creatine and creatinine metabolism may be affected under conditions of increased muscular tonus. The experiments of Pekelharing and Van Hoogenhuyze,[6] in which such a condition was induced by the electric current, caffein, nicotine, and calcium chloride, indeed indicate increased creatine metabolism. The same results were obtained with strychnine, cocaine, and alcohol by Van Hoogenhuyze and Verploegh.[7] Similar studies were also made in organic disease of the muscles by Spriggs[8] and by Levene and Kristeller,[9] but their results were not concordant. In disease of the nervous system Van Hoogenhuyze and Verploegh[7] have shown that creatine metabolism is highest in conditions of greatest excitement and lowest in depressive states. Since it has been established that caffein is a muscle as well as a nerve stimulant, its influence on creatine and creatinine metabolism seemed to be a proper subject for investigation. This was carried out on rabbits and dogs under different conditions of diet. It may be stated at the outset that, with few

exceptions, the results with caffein were negative in rabbits which were well fed; thus, even after the administration of large amounts of it no change in the elimination of creatine or creatinine was observed if liberal portions of carrots were fed. When the diet consisted of oats and cabbage, the creatine and creatinine constituents remained unchanged in most cases after the subcutaneous administration of caffein. Only when a large dose of 150 milligrams of caffein per kilo was administered was a moderate increase in the amount of creatine noticed in some experiments. The results in fasting rabbits and dogs will be given in the following pages.

Methods

Rabbits and dogs were the subjects used for the experiments in this investigation. The analyses were made on samples of urine formed in 24 hours or shorter periods. In rabbits the urine was obtained as follows: At the beginning of the experiment the bladder was emptied by means of external pressure of the abdomen and the urine thus obtained was discarded. The urine that was then voided spontaneously was collected in bottles containing thymol. At the end of the period the bladder was again emptied as before and the urine united with the portion collected. As some of the samples were exposed at room temperature for a part of the 24 hours it was considered advisable to make control observation on the possible decomposition or other changes which might be caused in the urinary creatine and creatinine, especially as the urine of rabbits was alkaline when fed carrots. Neither creatine nor creatinine was affected appreciably when urine was exposed at room temperature even for 24 hours.

In adult dogs the bladder was emptied by means of a catheter at the beginning of the experiment and at the end of each period. The elimination of creatinine was also studied in a number of young puppies. All the urines used for the analyses were voided spontaneously, neither the catheter nor pressure being used. The usual methods of analysis were employed. For creatine and creatinine the Folin method was used, while total nitrogen was determined by the Kjeldahl-Gunning method.

Experiments on Rabbits

Effect of Alkalinity of the Urine and of Temperature on Creatine and Creatinine.

The urines were obtained from rabbits which had been on an oat and cabbage diet. At the time of collection the urines were acid; thymol was used as a preservative.

Urine I

A. Examined immediately after collection (24 hours or less) at room temperature:

Total creatinine	125 mg.
Creatinine (preformed)	113
Creatine	12

B. Made alkaline with potassium carbonate and sodium carbonate and examined at the end of 96 hours at room temperature:

Total creatinine	131
Creatinine (preformed)	118
Creatine	13

Urine II

A. Examined immediately after collection:

Total creatinine	205
Creatinine (preformed)	171
Creatine	34

B. Made alkaline with sodium carbonate and potassium carbonate and examined at the end of 96 hours in the refrigerator:

Total creatinine	205
Creatinine (preformed)	171
Creatine	34

Urine III

A. Examined immediately after collection:

Total creatinine	99
Creatinine (preformed)	99
Creatine	0

B. Preserved at its normal reaction in refrigerator, 24 hours:

Total creatinine	99
Creatinine (preformed)	95
Creatine	4

URINE IV

A. Examined immediately after collection:	
Total creatinine	133
Creatinine (preformed)	118
Creatine	15
B. Preserved at its normal reaction at room temperature, 24 hours:	
Total creatinine	133
Creatinine (preformed)	120
Creatine	13

URINE V

A. Examined immediately after collection:	
Total creatinine	82
Creatinine (preformed)	82
Creatine	0
B. Made strongly ammoniacal and preserved at room temperature for 24 hours:	
Total creatinine	81
Creatinine (preformed)	81
Creatine	0

FASTING RABBITS

Having found, as stated above, that the metabolism of creatine and creatinine in well fed rabbits was unchanged after the administration of caffein, its effect on this process in starvation was put to an experimental test. This was considered desirable in view of the possible modification of the action of caffein in this condition, but more especially on account of the relation which was shown recently to exist between creatine metabolism and carbohydrate feeding. The experiments conducted on three rabbits, which received 150 milligrams caffein per kilo, are given in Table I.

It will be observed that in every case the elimination of creatine increased enormously during the 24 hours immediately following the injection of caffein and persisted on the following day. Creatinine was not affected to any appreciable extent. In all cases there was a slight tendency to increased elimination, but the increase amounted to a few milligrams only.

TABLE I

THE ELIMINATION OF CREATININE AND CREATINE IN FASTING RABBITS

RABBIT 885 (gray female)

Exp. and date	Weight gm.	Water consumed c.c.	Volume of urine c.c.	Feces	Caffein injected subcutaneously mg. per kilo	Albumin	Dextrose	Total nitrogen gm.	Total creatinine mg.	Preformed creatinine mg.	Creatine mg.
Sept. 26 [1]	1900										
Oct. 1	1600	60	80	none		none	none	0.968	101	78	23
" 2	1555	60	70	none	150	none	none	1.847	92	76	16
" 3	1530	50	120	none		none	none	1.325	195	86	109
" 4	1445	50	60	none		+	none	.804	121	73	48
" 5	1415	50	60	+		none	none	.747	88	67	21
" 6	1310	60	80	++		none	none	—	115	79	36

RABBIT 887 (gray male)

Sept. 26 [1]		2025										
Oct.	1	1800	60	65	none		none	none	1.142	101	86	15
"	2	1755	40	60	none	150	none	none	1.026	101	86	15
"	3	1590	50	135	++		none	none	1.314	195	92	103
"	4	1625	65	60	none		none	none	.846	160	80	80
"	5	1580	45	60	++		none	none	.915	128	77	51
"	6	1525	40	65	+++		none	none	—	125	74	51

RABBIT 888 (gray male)

Sept. 26 [1]		2700										
Oct.	1	2555	75	70	none		none	none	1.185	126	115	11
"	2	2605	60	65	none	150	none	none	1.120	120	120	—
"	3	2405	70	135	+		none	+	1.895	307	127	180
"	4	2370	70	115	none		none	none	1.651	193	125	68
"	5	2225	70	50	none		none	none	1.212	122	101	21
"	6	2140	80	55	none		none	none	—	109	84	25

[1] Food withdrawn.

TABLE II

B. Fasting Rabbits Receiving Varying Sized Doses of Caffein

Rabbit 941 [1]

Exp. and date	Weight of rabbit gm.	Water consumed c.c.	Volume of urine c.c.	Caffein injected subcutaneously mg. per kilo	Total nitrogen gm.	Total creatinine mg.	Preformed creatinine mg.	Creatine mg.	Symptoms
Dec. 3	2110		[2]						
" 4	2105	125	75	50	0.4680	50	47	3	—
" 5	2025	200	270	—	1.6380	183	89	94	none
" 6	1985	100	160	150	1.3480	122	111	11	—
" 7	1845	180	250	—	1.5996	157	82	75	Good; while pronounced, were not as exaggerated as those following a previous similar dose in the same animal (see table in Series VII); no albumen or dextrose present at any time in the urine.
" 8	—	100	108	—	.8360	131	72	59	—
" 9	1715	20	40	—	.3120	56	39	17	—

RABBIT 942 [1]

Dec. 3	2110								
" 4	2210	170	150	50	1.2950	92	90	2	—
" 5	1945	200	325	—	1.5127	197	97	100	none
" 6	1970	200	200	150	1.2000	157	108	49	—
" 7	1845	200	260	—	1.0664	112	57	55	Good; while marked, were not as strong as on the first dose of 150 gm. per kilo (see table in Series VII); no albumen or dextrose present.
" 8	—	200	209	—	1.0740	156	82	74	—
" 9	1750	70	80	—	1.1370	140	74	66	—

RABBIT 945 [1]

Dec. 3	2415								
" 4	2405	50	80	50	1.4740	123	92	31	—
" 5	2320	190	150	—	1.3750	117	81	36	none
" 6	2305	60	80	150	1.2100	99	89	10	—
" 7	2085	200	400	—	1.5000	143	92	51	Well marked, though not as exaggerated as after the first dose a week before (see table in Series VII); no sugar present at any time; albumen present throughout.
" 8	—	100	69	—	.9240	124	77	47	—
" 9	2065	60	60	—	.9768	130	85	45	—

[1] Fasted from December 3 to 9, inclusive. [2] Bladder emptied; urine rejected.

The total nitrogen varied from day to day. Diuresis may be assigned as a cause of the rise in the output of creatine; but this is contradicted by the fact that the creatine was high in the after period of the experiments on Rabbits 885 and 887, although the urine was normal in amount in both cases. As the striking results obtained in Rabbits 885, 887, and 888 might be due altogether to the size of the dose employed, additional experiments to test the influence of smaller doses of caffein in starvation were carried out on three rabbits, which received 50, 100, and 150 milligrams of caffein per kilo respectively. The results in all cases, both as regards creatine and creatinine, as well as total nitrogen, were negative. The conflicting results thus obtained might be accounted for by the greater resistance of these rabbits, since 150 milligrams of caffein per kilo did not produce increased reflexes and photophobia, which such a dose generally does. The work of Pekelharing and Van Hoogenhuyze, who found that increased muscular tonus stimulated creatine and creatinine metabolism, would indeed justify such an explanation. This suggestion was not borne out, however, by further tests as shown in the experiments 941, 942, and 945, Table II.

The subcutaneous injection of 50 and 150 milligrams of caffein per kilo in these rabbits was followed by a very marked increase in the elimination of creatine. The creatine was increased in Rabbit No. 941 when 50 milligrams caffein were injected, but decreased after a larger dose. This was also the case in Rabbit No. 942. In Rabbit No. 945 creatinine elimination was not affected by caffein when small or larger doses were given, which thus would seem to contradict the above experiments. The elimination of total nitrogen shows considerable irregularity with some tendency perhaps towards increased protein catabolism after the administration of caffein. Attention may be called here to the tables of Rabbits 885, 887, and 888 (Table I), and of 941, 942, and 945 (Table II), which show that the initial amounts of creatine were small or practically insignificant. With one exception caffein produced a decided effect on creatine elimination in these experiments, while in those experiments on starving rabbits in which the results were negative considerable amounts of creatine were found in the urine before the injection of caffein.

The relation of these findings to the increased elimination of creatine in the urine will be discussed later.

Elimination for Short Periods

Since all the preceding experiments were conducted on 24-hour samples, it seemed that in some cases the effect of caffein might be masked, especially when the action is not marked. Experiments were, therefore, carried out on rabbits from which the urine was obtained approximately at 3-hour intervals.

The data given in the table show that 150 milligrams caused a decided increase in creatine in two of the three rabbits, but had no effect on creatinine elimination. Doses of 50 milligrams of caffein per kilo were also tried in three other rabbits, but the results were negative.

Experiments on Dogs

That creatine as well as creatinine metabolism in the dog is quite different from that in the rabbit appears from the work of several observers. Richards and Wallace [10] found large amounts of creatine (160 milligrams nitrogen per day in the form of creatine) in the urine of a well fed dog, the creatinine nitrogen being 137 milligrams a day in the same subject. In another dog, which fasted, the creatine nitrogen was only about 40 per cent of the amount present in the well fed dog, the weight of each being about equal.

Underhill and Kleiner [11] in their experiments on fasting dogs reported practically the same amounts of creatine on the first as on the thirteenth day of the starvation, while considerable variation in the urinary creatine and creatinine was observed in the intervening period.

According to Hawk [12] and his co-workers, who experimented on a dog which fasted 117 days, creatine and creatinine diminished with the progress of the fast. The influence of caffein on creatine and creatinine elimination in dogs was, to our knowledge, never studied before. Since these animals react to caffein differently from the rabbit, as shown by Salant and Rieger,[13] experiments on its effect on creatine and creatinine metabolism were undertaken. Adult dogs and young puppies were employed.

TABLE III

THE ELIMINATION OF CREATINE AND CREATININE FOR SHORT PERIODS

RABBIT 941 [1]

Experiment and date	Weight of rabbit gm.	Water consumed c.c.	Volume of urine c.c.	Caffein injected subcutaneously mg. per kilo	Period mg.	Total creatinine mg.	Preformed creatinine mg.	Creatine mg.	Remarks
Nov. 30	2270	—	20	150	9:30 12:50	12.7	12.7	none	
		—	35	—	12:50 3:30	[2]	[2]	[2]	Very hypersensitive; photophobia.
		70	40	—	3:30 6:55	20.0	11.75	8.25	do

Rabbit 942									
Nov. 30	2180	—	9	150	9:40 12:40	16.2	14.0	2.2	
		—	40	—	12:40 3:45	[2]	[2]	[2]	Very hypersensitive; photophobia.
		20	15	—	3:45 7:05	12.0	11.3	.7	
Rabbit 945									
Nov. 30	2610	—	—	150	10:00 1:00	12.0	12.0	none	
		—	68	—	1:00 3:50	15.0	11.4	3.6	Very hypersensitive; photophobia.
		20	35	—	3:50 7:20	22.0	15.5	6.5	

[1] Diet oats and cabbage before experiments. None eaten on day of experiment.
[2] Out of range.

TABLE IV

ELIMINATION OF CREATINE AND CREATININE IN ADULT FASTING DOGS

DOG 55 [1]

Experiment and date	Weight of dog gm.	Water consumed c.c.	Volume of urine c.c.	Reaction of urine	Temperature F°.	Caffein injected subcutaneously mg. per kilo	Total nitrogen [2] gm.	Total creatinine mg.	Preformed creatinine mg.	Creatine mg.
Aug. 5	1200	250	100	—	—	50	—	352	330	22
" 6	1190	235	100	—	—	50	—	431	355	76
" 7	1160	185	115	—	—	50	—	324	305	19
" 8	1150	285	110	—	—	—	—	350	350	0
" 9	1140	130	125	—	—	—	—	332	316	16
" 10	1130	95	100	—	—	—	—	294	278	16

Dog 117										
Dec. 11	117	175	90	acid	101	none	2.6880	198	160	38
" 12	—	45	—	acid	—	none	1.8183	259 [3]	158 [3]	101
" 13	—	92	—	acid	101.2	100	—	—	—	—
" 14	—	92	160	acid	101.2	none	2.3160	256	156	100
" 15	—	92	60	acid	101.2	none	2.2080	221	190	31
" 16	—	92	55	acid	100.6	50	2.6820	276	167	109
" 17	—	92	72	acid	100.4	none	2.5768	196	158	38
" 18	—	92	54	acid	99.6	none	—	191	158	33
" 19	—	92	80	acid	100.5	none	2.4600	143	125	18

[1] Had been on full meat diet until August 3 when fasting was begun.
[2] Determined by T. C. Trescot, nitrogen laboratory.
[3] Average.

The subcutaneous injection of 150 to 250 milligrams of caffein per kilo into puppies which were fed milk exclusively failed to show any effect on creatine. Experiments on three adult dogs, two of which received caffein in starvation, proved negative whether small or large doses were given. Dog 117, which received 100 milligrams of caffein per kilo subcutaneously, showed much irregularity in the elimination of creatine, the elimination of creatinine being on the contrary quite regular and unaffected. The total nitrogen likewise remained unchanged in this case.

It was pointed out on page 194 that caffein stimulated creatine metabolism in rabbits only when the amounts present in the urine were small. This observation suggests an explanation of the seemingly conflicting results obtained. It has been shown by Fujitani [14] and Hattori [15] that caffein stimulates proteolytic enzymes. It may be inferred that other enzymes are influenced in the same way. Increased glycogenolysis due to caffein would, therefore, seem probable. Richter [16] has indeed shown that caffein and its allied products decrease hepatic glycogen in rabbits which received a rich carbohydrate diet. The glycosuria and hyperglycemia under these conditions lend support to this view. A relation having been shown to exist between creatine and carbohydrate metabolism by Taylor,[17] Mendel and Rose,[18] and others, increased elimination of creatine may be expected after the administration of caffein. The negative results, however, obtained with caffein in carrot fed rabbits would seem to contradict this view. But in this connection it is important to bear in mind that the larger amount of glycogen in the body found after an abundant diet of carrots may account for the failure to stimulate the elimination of creatine. It is conceivable that the amount of glycogen transformed was insufficient to disturb creatine metabolism. Moreover, it is quite probable that in starvation the glycogen residue is more easily destroyed under the influence of caffein, thus leading to an increased elimination of creatine in the urine. On the above supposition the elimination of creatine would not be affected by caffein when the store of glycogen has been depleted, since its action on creatine is exerted through the intermediation of glycogen. If the amounts of creatine in the urine may be considered an index of the store of glycogen present in

the body, it is evident that small amounts of creatine in the urine indicate a sufficient amount of glycogen in the body, large amounts of creatine indicating, on the contrary, little or no glycogen in the body. The conflicting results obtained can now be explained. In Table I the amounts of creatine were small in the fore-period, being 11 milligrams in Rabbit 888 on the first day; in the second fore-period none was found. It is significant that in this experiment the creatine eliminated after the administration of caffein was about 80 per cent higher than in either of the other two of this group. The results in Table II may be similarly explained. In Rabbits 941 and 942 insignificant amounts of creatine were found in the urine of the control period. The administration of 50 milligrams per kilo was followed by an enormous increase in the elimination of creatine. The same was observed in the next rabbit. In No. 945 there was a moderate amount of creatine in the urine of the fore-period, but in this case it will be noticed that the same amount of caffein in proportion to body weight as in the other two rabbits of this series was without effect. The experiments with larger doses may be explained in the same way. It will be noticed that here also the urinary creatine increased as a result of the administration of caffein only when the initial amounts of creatine were small, as shown in a striking manner in Rabbits 941 and 945. On the other hand, in Rabbit 942, in which the amount of creatine before the injection was moderately large, no change in the urinary creatine was observed. In Rabbits 941 and 945 the amounts of creatine before the injection were 10 and 11 milligrams respectively, but after injection they rose to 75 milligrams in one and 51 milligrams creatine in the other.

Of particular interest is the elimination of total nitrogen. Notwithstanding the size of the doses employed and the symptoms of intoxication produced, protein metabolism was not affected by caffein either in the rabbit or in the dog. These results are in striking contrast to those obtained by Ribaut,[19] who reported an extensive series of experiments on the influence of caffein on protein metabolism in dogs. By the administration of small doses of caffein he was able to produce diminution, but with larger doses, augmentation, of the nitrogen output. The

data in some of these experiments clearly show that the differences in the elimination of nitrogen are within the limits of experimental error.

Résumé and Conclusions

Medium doses of caffein given to rabbits on a diet of oats may stimulate slightly the elimination of creatine. No effect on creatine or creatinine was observed with caffein in rabbits which were fed sufficient amounts of carrots. The elimination of creatine may be marked in starving rabbits after the administration of 50 to 150 milligrams of caffein per kilo. But this was not found to be universally the case in such animals. Evidence was brought forward showing that caffein disturbs creatine elimination by acting upon glycogen metabolism. Total nitrogen was not influenced in starving or well fed rabbits after the administration of caffein. Caffein had no effect on the elimination of creatine and creatinine or total nitrogen in adult fasting dogs, nor on creatinine in young, well fed puppies. The difference in the effect of caffein observed in these animals is probably due to a difference in the amount and rate of transformation of glycogen. Since it is more readily decomposed in the rabbit, caffein simply stimulates this process and thus depletes the store of glycogen in the liver and probably also in the muscles; hence, creatine is eliminated in larger amounts.

The important conclusions to be drawn from the above results are:

1. That stimulation *per se* of the nervous system or muscles or both does not seem to affect creatine or creatinine metabolism, nor the excretion of total nitrogen, the evidence here presented tending to indicate rather that the effects observed may be due primarily to acceleration of enzyme action, which causes the transformation of glycogen.

2. *The data obtained in the present investigation show that the effect of a substance on protein metabolism is not a safe guide for drawing inferences regarding its toxicity.*

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THRESHOLDS FOR FARADIC STIMULATION OF THE RESPIRATORY REFLEX AND OF THE PHRENIC-DIAPHRAGM PREPARATION

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THIS study was undertaken to measure the threshold stimuli for the respiratory reflex on exciting the central end of a vagus nerve and to determine the thresholds for the phrenic-diaphragm preparations. The strengths of stimuli were measured by Martin's[1] method. This is one of a series of quantitative investigations in progress in this laboratory.

Methods

The animals used in these experiments were chiefly decerebrate cats. A few rabbits were also studied and some readings were made on the nerve-muscle preparations of urethanized cats. The decerebration was done under ether narcosis. After decerebration the anaesthetic was dispensed with, the animal continued to breathe, and the respiratory reflexes could be evoked. This method appears to be the most satisfactory for studying this reflex in its normal condition. The temperature of the animal was maintained by an electric heating pad.

In order to obtain a record of the respiratory muscle movements in response to minimal stimuli, both for the reflex and for the direct nerve-muscle preparation, various devices were tested. Head's diaphragm slip method[2] proved to be too insensitive to record responses to threshold stimuli in the cat. The same

[1] Martin: The measurement of induction shocks, New York, 1912; also this journal, 1908, xxii, p. 116, and 1910, xxvii, p. 226.

[2] Head: Journal of physiology, 1889, x, p. 1; also Barry: Journal of physiology, 1913, xlv, p. 473.

difficulty was found with a tambour connected with a T-cannula in the trachea.

The method of recording which proved effective was the attachment of an S-shaped hook to the diaphragm about half way between the central tendon and the lateral chest wall. From this hook a thread was passed over a pulley to a writing lever.

Similar preparations were made to record movements of the chest wall. It was found, however, that the chest wall moved synchronously with the diaphragm or did not move at all, so the recording was restricted to the diaphragm alone.

To determine minimal reflex stimuli a Sherrington shielded electrode was placed on the central end of a divided vagus nerve. The movements of the diaphragm were recorded for a few minutes. When the character of these movements had proved fairly uniform, a series of break shocks were sent through the nerve and the record observed for changes. The secondary coil was first placed at about 30 cm. distance from the primary. If no change was produced, the coil was shoved 1 cm. nearer the primary and a second series of shocks delivered. This procedure was continued until a change could be observed in the recorded movements, consisting usually of a slight shallowness of breathing followed by an increase in the depth. The secondary coil was now pushed out .5 cm. and the test repeated. If no change in breathing occurred, the secondary coil was pushed in 1 mm. at a time and stimuli sent into the nerve until the threshold was found. Then the threshold was separately determined with 10,000, 20,000, and 30,000 or 40,000 ohms in the secondary circuit with the nerve. To avoid summation, care was taken to allow an interval of 15 to 20 seconds between the successive series of stimulations.

After the four thresholds with the different resistances had been determined, the nerve was thrown into circuit with a Wheatstone bridge and the tissue resistance measured by the Kohlrausch method.

Both vagi were never cut in the same animal in determining the threshold for the reflex. After the threshold for the reflex was found, the thresholds for the phrenic-diaphragm prepara-

tions were investigated. In order to obtain these, either one phrenic nerve was divided near its entrance into the thorax, and its peripheral end placed in a Sherrington shielded electrode, or the nerve was not severed but a special platinum electrode[1] was hooked onto it and shielded from the surrounding tissues by rubber. No differences in the values of the threshold units were observed in using the different electrodes.

TABLE I

PROTOCOL

RIGHT PHRENIC. EXPERIMENT I. JULY 19, 1912

DECEREBRATE CAT. OPERATED 10.30 A.M. READINGS BEGAN 11.15 A.M.

	Tissue	10,000 ohms	20,000 ohms	30,000 ohms	Average
Total resistance in the secondary circuit	40,900 ohms	50,900 ohms	60,900 ohms	70,000 ohms	
Primary current	0.2 ampere	0.2 ampere	0.2 ampere	0.2 ampere	
Secondary position	37.9	36.6	34.9	34.2	
$\frac{M}{L}$	23.2	26	29.4	31.8	
Z	4.64	5.2	5.88	6.36	Plots a straight line
A		4,200	3,400	4,100	3,900
β	2.28	2.27	2.29	2.26	2.27
R Known	20,000 ohms	30,000 ohms	36,000 ohms	R coil	
R Calculated	34,100 ohms	41,500 ohms	42,500 ohms	1,400 ohms	40,900 ohms

For calling forth the reflex contractions, a series of twenty shocks (five per second) was sent through the nerve in the early experiments. Later this number was increased to thirty. In determining the threshold of the phrenic-diaphragm preparation single induction shocks were used. It was planned to obtain a series of readings for the respiratory reflex and then to ascertain the threshold of both phrenic-diaphragm preparations on each

[1] CANNON and NICE: This journal, 1913, xxxii, p. 44.

animal studied. This was not often accomplished, however, since considerable time was required to obtain the necessary data for calculating the β units. After a time, usually three to five hours, the respiratory movements in decerebrate cats became very irregular or paralysis of the respiratory mechanism would occur. This irregularity and paralysis seem to be due to extravasated blood pressing on the bulb.[1] As soon as the breathing began to be irregular, no more readings were taken on the reflex. The strength of stimuli was measured in β and Z units.

In Table I, the data and calculated results of a single experiment are set forth.

To obtain a series of readings for the respiratory reflex usually required 30 to 45 minutes; for the phrenic-diaphragm preparation 10 to 15 minutes. The readings were never begun on an animal until 30 or 40 minutes after decerebration. This lapse of time was to permit the effects of the ether to pass off before studying the reflex.

Results and Discussion

The data secured in these experiments are set down in Table II.

Examination of the table shows the relation of the average values of β on the two sides of an animal. The average of β for the left phrenic-diaphragm preparation is 1.89; for the right, 1.33. The average values determined for Z on the two sides are 3.41 for the left and 3.14 for the right. These values are somewhat higher than the thresholds reported by E. L. Porter in stimulating the peripheral end of the radial nerve in cats.[3] He obtained an average of 1.4 for β and 2.3 for Z.

The threshold for the respiratory reflex gave an average value of 2.52 (nine observations on the left vagus) and 2.87 (eight observations on the right vagus) for β; and 4.12 (fifteen observations on the left vagus) and 4.59 (ten observations on the right vagus) for Z. On account of the necessity of leaving

[1] Forbes: Quarterly journal of experimental physiology, 1912, v, p. 149.

[2] Martin: *Loc. cit.*

[3] Porter, E. L.: This journal, 1912, xxxi, p. 148.

TABLE II

THE THRESHOLD STIMULI OF THE RESPIRATORY REFLEX AND OF THE PHRENIC-DIAPHRAGM PREPARATIONS MEASURED IN Z AND β UNITS

		Phrenic		Phrenic		Vagus		Vagus	
Date	Animal	Left Z	Right Z	Left β	Right β	Left Z	Right Z	Left β	Right β
July 12	cat	1.54	1.80	1.30	1.35				
" 12	"		2.30						
" 19	"		4.64		2.27				
" 22	rabbit	1.54	1.87	1.30	0.85				
" 23	cat	5.70	6.00		0.65				
" 27	"	4.10					1.35		1.30
Aug. 2	"		2.85		2.08				
" 4	"	4.20		3.18			5.60		4.28
" 8	"	5.29		4.29					
Oct. 22	"	4.36	1.43	2.19					
" 24	"					6.66		5.94	
Nov. 4	"	1.10	4.76	0.32	0.38			3.01	
" 11	"		1.45						
" 11	"		1.48						
" 12	"					8.40		1.25	
" 18	rabbit	1.89	1.89			7.84		2.34	
" 20	cat		1.93		1.67				
" 21	"		7.70						
" 22	"		1.93						
" 23	"		2.84		1.34				
Feb. 11	"						1.11		
" 22	"		2.00			1.70			
Mar. 29	"	1.48	0.56	0.67			3.70		2.64

TABLE II — *continued*

Date	Animal	Phrenic		Phrenic		Vagus		Vagus	
		Left Z	Right Z	Left β	Right β	Left Z	Right Z	Left β	Right β
Apr. 16	Cat	3.52				2.84			
" 17	"	5.43				10.05			
" 17	"					9.10		6.68	
" 26	"		7.35				11.00		4.66
May 10	"	4.20				3.25			
" 10	"					3.20			
" 10	"					2.84			
" 10	"					2.48			
" 17	"		2.05		1.31		2.35		1.26
" 17	"		3.15		1.40				
" 17	"		3.21						
" 17	"		4.05						
" 17	"		4.00						
" 17	"		3.70						
" 7	"		3.60						
Aug. 23	"						5.60		2.43
" 23	"						9.00		4.80
" 23	"						4.65		1.63
" 23	"						1.60		
" 25	"					1.30		1.26	
" 25	"					.90		.93	
" 28	"					.61		.61	
" 28	"					.72		.71	
Average		3.41	3.14	1.89	1.33	4.12	4.59	2.52	2.87

one vagus intact, direct comparisons of right and left vagi could not be made. Porter obtained an average value of 2.7 for β and 5.7 for Z in a study of the flexion reflex in the hind limb of the cat.[1]

In studying the respiratory reflex, changes of threshold occurred so often that in rabbits and in many of the cats it was impossible to obtain the β units.

In comparing the average values of β and Z, both for the nerve-muscle preparations and for the reflex, no marked differences are observed in the amount of their variations. The relative values of these units, however, have been shown to be decidedly in favor of the β units for accurate measurements.[2]

An examination of the separate cases reported in Table II shows that there is wide variation in the threshold values. In general, however, the units obtained on the left and right phrenic nerves in the same animal correspond fairly closely. The cat studied July 12 gave a β of 1.3 for the left phrenic-diaphragm preparation and 1.35 for the right; the rabbit observed July 22 gave a value of 1.3 for β on the left phrenic and .85 for the right; while on November 4 the β for the left phrenic in the cat was .32 and for the right .38.

As for the values of the Z units, in some cases they agree approximately in the same animal, but in others there is considerable difference. For example, on July 23 the left phrenic-diaphragm preparation in a cat gave a value for Z of 5.7, the right 6.0; on November 18 the Z's for the left and right phrenic in a rabbit were the same, — 1.89. On the other hand, the cat studied October 22 had a Z of 4.36 for the left phrenic-diaphragm preparation and 1.43 for the right; on November 4 a cat gave 1.10 for the left and 4.76 for the right phrenic-diaphragm preparation.

How the respiratory reflexes in decerebrate animals compare with those in animals under different degrees of anaesthesia requires further study. More work is also necessary to determine whether there are in the thresholds for the respiratory

[1] Porter: *Loc. cit.*

[2] Martin: *Loc. cit.*; also Martin, Porter, and Nice: The psychological review, 1913, xx, p. 194.

movements of animals under anaesthetics irregularities similar to those observed in decerebrate animals.

The threshold value of the phrenic-diaphragm preparation was the same in decerebrate animals and in those anaesthetized with urethane. These results are in accord with those of E. L. Porter for the wrist extension.[1]

Summary

1. This study was made to determine the threshold value of Faradic stimulation for the respiratory reflex, elicited by exciting the central end of a vagus nerve; and to measure the thresholds for the phrenic-diaphragm preparation.

2. The average threshold stimulus for the left phrenic-diaphragm preparation (thirteen observations) was 3.41 in Z units; for the right (twenty-five observations), 3.14.

3. The average threshold stimulus in β units for the left phrenic-diaphragm preparation (seven observations) was 1.89; for the right (ten observations), 1.33.

4. The average threshold stimulus for the respiratory reflex when the central end of the left vagus was stimulated (fifteen observations) was 4.12 in Z units; for the right vagus (ten observations), 4.59.

5. The average threshold stimulus in β units for the respiratory reflex, found by stimulating the central end of the left vagus (nine observations), was 2.52; for the right (eight observations), 2.87.

[1] *Loc. cit.*

VASOMOTOR REFLEXES FROM THRESHOLD STIMULATION

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WE wish to report in this paper some observations on blood-pressure changes brought about by the central stimulation of various severed spinal nerves with induction shocks of known intensity. So far as we are aware, the only important studies hitherto of vasomotor responses to measured sensory stimuli are those of W. T. Porter and his co-workers.[1] These investigators used an inductorium with Kronecker graduations. Their stimuli are expressed, therefore, in Kronecker units. For actuating their inductorium a Daniell cell of known voltage (1.1 volts) was used. By the exercise of great care in experimentation and by the accumulation of a large number of results they eliminated "accidental errors" and were able, therefore, to draw sound and valuable conclusions.

The method of measuring stimuli adopted by them, while valuable for securing such data as they sought, does not afford a basis for comparison of their stimuli with those that would be required to bring about other physiological effects. In the belief that comparisons of the stimuli used in various fields of physiological experimentation would prove valuable, we undertook the present study.

Methods. — For measuring our stimuli the method devised by one of us[2] was employed. By this method the strengths of stimuli may be expressed in Z units,[3] the equation for Z being

[1] For a summary of this work, with references, see W. T. Porter: This Journal, 1910, xxvii, p. 276.

[2] Martin: The measurement of induction shocks, New York, 1912.

[3] Martin: *Loc. cit.*, p. 73; also this Journal, 1910, xxvii, p. 228.

$$Z = \frac{M}{L} I,$$

in which $\frac{M}{L}$ is determined by the position of the secondary coil in a properly calibrated inductorium, and I is the intensity of the primary current in amperes. When Z units are used, no account is taken of the electrical resistance of the secondary circuit, nor of the influence of the manner of contact of the stimulating electrodes. While doubtless a certain error enters when these factors are neglected, the studies of Martin,[1] confirmed by the later experience of ourselves and others, show that when a uniform procedure is employed the error is unimportant for the purposes of such an investigation as this. Moreover, stimuli expressed in Z units can be duplicated much more readily than when the complex corrections required for great exactness [2] are introduced. For these reasons we have felt justified in employing Z units throughout this work.

Our experiments were performed upon cats. For anaesthetization we used decerebration, according to the method brought to this laboratory from Sherrington by Forbes;[3] brain compression, according to Hunt;[4] cerebral pithing, by means of a sharp instrument through the orbit; ether; and urethane. Blood pressures were registered by a mercury manometer connected with one of the carotid arteries. For sensory stimulation the radial, median, ulnar, sciatic, and saphenous nerves were used. Stimuli were applied by means of platinum electrodes. The nerves undergoing stimulation were protected by glass shields similar to those described by Sherrington.[5] For making and breaking the primary circuit a vulcanite knife-blade key [6] was so arranged that the revolutions of a small motor made and broke the circuit two to eight times a second. When more rapid rates of stimulation were desired a motor-driven interrupter with platinum contacts was used. With this latter appara-

[1] Martin: The measurement of induction shocks, p. 82.
[2] Martin: *Loc. cit.*, p. 73.
[3] Forbes: Quarterly journal of experimental physiology, 1912, v, p. 163.
[4] Hunt: Journal of physiology, 1895, xviii, p. 383.
[5] Sherrington: Journal of physiology, 1909, xxxviii, p. 382.
[6] Martin: *Loc. cit.*, p. 63.

tus stimuli could be sent in at rates of from four to sixty a second.

Data on which to Base Comparisons. — Thus far not many series of observations have been reported in which sensory stimuli have been applied quantitatively to mammalian nerves according to the method used by us. One such is a series of measurements of the threshold of the flexion reflex in spinal cats by E. L. Porter.[1] This investigator made a considerable number of observations and obtained an average threshold of 5.2 Z units (*loc. cit.*, p. 149). In only four of his fifty-six cases did the threshold exceed 10 Z units, and in only four was it less than 2 Z units. These limits, two to ten units, may be taken, then, to represent with reasonable accuracy the intensity of a stimulus, applied directly to a nerve trunk containing sensory fibres, which suffices to elicit demonstrable activity within the central nervous system, in unanaesthetized mammals.

Forbes,[2] using decerebrate cats, has employed stimuli, measured in Z units, for inducing reflex excitation and inhibition. His experiments usually called for stimuli well above the threshold. Such stimuli, as reported by him, had strengths ranging from 5.5 to 37 units, except where his procedure called for markedly powerful stimuli.

A criterion of stimulation strength that has been much used in the past is the threshold of perception when a pair of platinum electrodes is placed against the tongue. To gain some idea of the value of stimuli which satisfy this criterion, we have determined, on a number of individuals, the value in Z units of stimuli reported by them as thus barely perceptible. Our results show surprisingly little variation. Nearly all our subjects considered a stimulus of 80 units just above the threshold for tongue perception. This is a stimulus approximately sixteen times as strong as will suffice to elicit the flexion reflex when applied directly to a nerve trunk.

Vasomotor Reflexes Uncomplicated by Drug Anaesthesia. — Our first study was of the effect of sensory stimulation upon

[1] E. L. Porter: This journal, 1912, xxxi, p. 141.

[2] Forbes: *Loc. cit.*, p. 165; also Proceedings of the Royal Society, 1912, lxxxv, p. 290.

blood pressure in animals rendered unconscious by means not involving the administration of drugs — brain pithing, decerebration, or brain compression. To avoid drug complications completely the animals were not curarized. Obviously these conditions call for the employment of weak stimuli only, since powerful ones, by eliciting vigorous reflex movements, would be likely to induce blood-pressure changes of mechanical origin such as might obscure completely any true vasomotor reactions.

Table I is a summary of the results of eight experiments performed under the conditions outlined above. Of the thirteen stimulations there recorded, only one exceeded a value of 16 Z units. The average value of all the stimuli was 8.7, signifying that they were well within the range of values cited above (p. 214) as representing stimuli barely able to arouse activity within the central nervous system. Every one of these stimulations, save one on April 23, produced a definite *drop* in blood pressure. The rise in pressure reported on April 23 we wish to note as the only instance in our experience, comprising several hundred stimulations at or near the threshold for spinal cord activity, in which a rise in pressure followed such threshold stimulation. The reaction in that exceptional case disappeared within fifteen minutes from the beginning of the experiment.

That the drop in pressure, characteristic for stimuli near the threshold, is a marked one, is shown in Fig. 1, which is the record of the effect on blood pressure of a stimulus of 7.6 units. The experiment was that of April 2. The cat was decerebrate, and the nerve stimulated was the radial. In the same experiment the threshold was obtained with a stimulation of 3.84 units. The thirteen stimulations given in Table I represent the weakest stimuli which gave unmistakable blood-pressure changes. In every one of the experiments the stimulation was repeated many times over a range of stimuli from the threshold value to three or four times the threshold. Well-marked drops of pressure followed all such stimulations, save in the exceptional experiment reported above.

In order that our animals might be as nearly normal as possible we usually left both vagus nerves intact. We assured ourselves repeatedly by careful counts of the heart rate before

TABLE I

BLOOD PRESSURE CHANGES INDUCED BY WEAK SENSORY STIMULATION IN ANIMALS RENDERED UNCONSCIOUS WITHOUT DRUG ANAESTHESIA

Date, 1913	Nerve	Pressure change	Strength of stimulus
Mar. 18	Sciatic	drop	9.1
" 25	Radial	"	1.28
Apr. 2	"	"	3.84
" 23	Sciatic	rise [1]	6.4
May 14	Radial	drop	5
July 25	Sciatic	"	31.5
" "	Median	"	11.2
" "	Ulnar	"	9.6
" "	Saphenous	"	2
" 30	Sciatic	"	15.4
" "	Ulnar	"	6.4
" "	Saphenous	"	5
Oct. 16	Sciatic	"	5
		Average	8.7

[1] This response was obtained only with three successive stimulations at the very beginning of the experiment. During the later stages stimuli of this strength produced no effect whatever.

and during the blood-pressure change that the change was not due to a change in heart rate. For further assurance we performed a number of experiments with both vagi severed. The drop in blood pressure following threshold stimulation was as definite in these experiments as in the ones with vagi intact.

That weak sensory stimulation may cause lowering of blood pressure was observed by Knoll.[1] That the blood-pressure lowering mechanism is to be included among the highly excita-

[1] KNOLL: Sitzungsberichte der Akademie der Wissenschaften zu Wien, Math.-Naturwiss. Klasse, 1885, xcii, Abtheilung 3, p. 449.

ble reflex mechanisms of the body could be definitely recognized only through the application of a basis of comparison such as was not available to Knoll. Our results seem to show clearly that this mechanism may properly be so classed. The observation of Kleen [1] that mechanical stimulation of muscles produces typically a fall of blood pressure seems to us strictly in harmony with our contention that

FIGURE 1. Effect on blood pressure of a stimulus of 7.6 Z units applied to the central end of a cut radical nerve. Decerebrate cat, uncurarized. Duration of stimulus, 20 seconds. Signal at atmospheric pressure base line.

FIGURE 2. Tracing showing blood-pressure fall in a cat under urethane anaesthesia without curare when the saphenous nerve was stimulated centrally. Stimulation strength 5 Z units. Duration of stimulus 30 seconds. Time signal corresponds to atmospheric pressure base line.

stimuli near the threshold for spinal cord activity have generally that physiological effect. The stimuli generated by his procedures must necessarily have been weak in comparison with induction shocks as ordinarily applied to naked nerves.

Contrary to the statement of Hunt [2] that the saphenous

[1] KLEEN: Skandinavisches Archiv für Physiologie, 1889, i, p. 247.

[2] HUNT: *Loc. cit.*, p. 386.

nerve in cats differs from other sensory nerves in that lowered blood pressure rarely results from its stimulation, we have been able to observe no difference in response between this and other nerves. In any experiment in which threshold stimulation of any sensory nerve brought about lowered blood pressure, similar stimulation of every sensory nerve included in our list of selected nerves (p. 213) yielded the same result.

Inasmuch as there is a tendency in general discussions of vasomotor reflexes to attribute purely pressor functions to cutaneous nerves,[1] we consider our results with the saphenous nerve specially significant. The extent of the pressure-drop which may be induced by weak stimulation of this nerve is illustrated in Fig. 2, which is the record of a tracing made on Oct. 29 from a cat under urethane anaesthesia. The strength of stimulus was 5 units.

The Influence of Drug Anaesthesia on the Reflex Pressure-Lowering Mechanism. — E. L. Porter [2] has shown that the threshold of an ordinary spinal reflex (flexion reflex) is promptly and markedly affected by the use of an anaesthetic drug (ether). Inasmuch as many, if not most, blood-pressure studies have been and are likely to continue to be carried on in animals anaesthetized by drugs, the question of the influence of anaesthetics upon the threshold for reflex blood-pressure change is an important one. We have here to report observations on the effects of ether and urethane. The influence of curare, a drug used almost invariably in blood-pressure researches, is now under investigation in this laboratory and will be reported in a subsequent paper.

The method of administering ether was that usually followed in this laboratory. The animal was tracheotomized and ether vapor allowed to mix with the inspired air at such intervals as the condition of the animal, as indicated by the corneal and abdominal reflexes, seemed to require. This method is obviously faulty in that it gives not a uniform depth of anaesthesia, but a succession of increasing and diminishing depths as the ether

[1] See, for example, STARLING: Principles of human physiology, Philadelphia, 1912, p. 1126.

[2] E. L. PORTER: This journal, 1913, xxxi, p. 226.

is applied and withdrawn. Our justification for using it is that it is so general in physiological practice that data obtained during its use are likely to be fully as valuable as any that might be had from experiments in which etherization is carefully maintained at a uniform level.

Urethane was administered by stomach tube about one half hour before beginning an experiment. Two grams per kilo body weight, dissolved in a small quantity of warm water, were given. The anaesthesia produced by this drug is very profound, whether judged by the usual criteria or by determining quantitatively the threshold for the flexion reflex. In connection with these experiments we have repeatedly stimulated sensory nerves with shocks exceeding 2000 Z units without eliciting perceptible reflex movements. The conditions of administration of the drug and the general behavior of animals under its influence indicate that it operates more uniformly than does ether as ordinarily employed. Exact information in this regard is wanting.

Table II contains the record of our determinations of thresholds of blood-pressure change under ether and under urethane. Drops of pressure were invariable at the strengths of stimulus used. The striking fact brought out by the table is the relatively slight extent to which the threshold for blood-pressure change is affected by the anaesthetics. Of twenty-three observations with ether only one had a threshold above 26 units. The average of the entire number is 14.7. Of eleven observations with urethane only one threshold above 22 appeared. The average of all urethane thresholds is 15.3. These average figures, when compared with the average threshold for animals without drug anaesthesia of 8.7 (p. 215), and with the affects of the same anaesthetics upon the threshold of the ordinary flexion reflex, indicate a much greater resistance to drugs on the part of the mechanism controlling blood pressure than is possessed by other portions of the central nervous system. Thus E. L. Porter's curve of the effect of ether on the flexion reflex threshold (*loc. cit.*) shows a six-fold increase of threshold following the administration of the drug. Our relatively crude observations cited above show that urethane may raise the same threshold several hundred-fold. Yet the threshold for blood-

TABLE II

THRESHOLD STIMULI FOR PRODUCING BLOOD-PRESSURE FALL IN CATS ANAESTHETIZED WITH ETHER OR URETHANE

Date, 1913	Anaesthetic	Nerve stimulated	Strength of stimulus
June 25	Ether	Radial	11
July 11	"	"	13
" "	"	Sciatic	25.5
" 21	"	Median	3.84
" "	"	Ulnar	8.7
" 23	"	Radial	8.7
" "	"	Sciatic	18
" "	"	Ulnar	25.5
" 25	"	Sciatic	13
" "	"	"	15.2
" 26	"	Radial	7.7
" "	"	Sciatic	13
" "	"	Ulnar	13
" 26	"	Saphenous	7.2
" 31	"	Sciatic	25.5
" "	"	Ulnar	8.7
Aug. 12	"	Sciatic	25.5
Oct. 3	"	"	22
" 15	"	"	8.4
" 20	"	"	11
" 23	"	Saphenous	2.75
" 24	"	"	35
" 27	"	Radial	15.4
			Average 14.7
July 3	Urethane	Sciatic	37.5
" 24	"	Radial	13
" "	"	Sciatic	21.5
" "	"	Median	11.2
" "	"	Ulnar	21.5
" "	"	Saphenous	7.7
Oct. 8	"	Sciatic	22
" 10	"	"	22
" 29	"	Saphenous	2.3
" 30	"	"	5
" 31	"	Ulnar	5
			Average 15.3

pressure fall is so little affected that doubling of the stimulation strength is ample to produce the change.

Is Blood-Pressure Rise or Blood-Pressure Fall the "Normal" Response to Sensory Stimulation? — If we may judge from the tenor of most general discussions of the subject,[1] the accepted doctrine in physiology regarding vasomotor reflexes is that "pressor" responses are usual, and typical for sensory nerves in general, while "depressor" responses are exceptional for all sensory nerves save the depressor nerve of the heart. Most writers, while adopting this general attitude, qualify it by specifying conditions under which one or the other response may be expected. Thus Hofmann[2] states in the same discussion in which he refers to them as usual (p. 325), that pressor responses follow *strong* stimulation. Starling (*loc. cit.*) assigns the production of pressor reflexes to the sensory nerves of the skin and to such impulses in general as would cause pain in the conscious organism. This belief in pressor responses as "normal" prevails side by side with general acceptance of the view, first supported experimentally by Latschenberger and Deahna,[3] and later confirmed by Hunt[4] and others, that sensory nerve trunks contain both "pressor" and "depressor" (reflex vaso-dilator) fibres. The idea that pressor responses are more normal to the organism than depressor ones appears to rest chiefly upon the observations of Hunt (*loc. cit.*, p. 381) that to replace pressor responses by depressor ones certain procedures are necessary, such as cooling the nerves, or allowing them to regenerate after section, or to be impaired by prolonged experimentation. While we have not repeated Hunt's studies with cooled or regenerated nerves, we have made comparisons between the responses given by freshly exposed nerves and those subjected to prolonged experimentation. We find that threshold stimuli applied to nerves immediately upon their exposure produce pressure-drops as certainly as in later stages of the

[1] See, for example, HOFMANN: Nagel's Handbuch der Physiologie des Menschen, Braunschweig, 1910, i, p. 322.

[2] HOFMANN: *Loc. cit.*, p. 322.

[3] LATSCHENBERGER and DEAHNA: Archiv für die gesammte Physiologie, 1876, xii, p. 165.

[4] HUNT: *Loc. cit.*, p. 390. For further references see HOFMANN: *Loc. cit.*

experiment. To assure ourselves of this fact we frequently made the test by means of ordinary electrodes placed upon the nerves at the moment they were dissected free, and without allowing even the brief delay involved in placing the Sherrington electrode in position. Hunt interpreted his results as signifying that by his procedures the pressor fibres were put out of function while the depressor fibres continued functional. An alternative and equally possible explanation is that the effect on the nerve trunks of Hunt's procedures was merely impairment of conductivity. Thus strong stimuli were converted into weak ones, and what Hunt observed was the usual effect on blood pressure of threshold stimulation, such as we have reported above. If this alternative explanation be accepted, we are reduced to the view that the nature of the response is determined by the strength of the stimulus, and our inquiry becomes one as to whether strong or weak sensory stimuli are more "normal" to the organism.

Thresholds for Pressor Reflexes. — Of service toward answering our question would be some idea of the strength of stimulation usually required to evoke a pressor reflex. The scope of the present investigation has not included a careful study of the pressor threshold, but in the course of our experimenting we have had repeated opportunity to note roughly the stimulation strength at which pressor responses appear. The average strength of stimulus for nineteen such stimulations on as many different nerves is 280 Z units.

Although most investigators in this field have described their stimuli in such fashion that no idea whatever of the strengths employed can be formed, fortunately W. T. Porter and his coworkers, already referred to (p. 212), describe their stimuli in terms translatable into the units with which we have worked. Their strengths of stimulation can be compared, therefore, with ours.

On page 278 of his paper W. T. Porter[1] publishes a curve of pressor reflexes plotted against stimulation strengths. His stimuli ranged from 250 to 2000 Kronecker units. While Kronecker units cannot, on account of a fault in the method of

[1] W. T. Porter: *Loc. cit.*

their preparation,[1] be converted directly into ours by computation, we have had the good fortune to be able to apply the Martin calibration to the particular inductorium with which W. T. Porter worked. On that apparatus 250 Kronecker units correspond with $\frac{M}{L} = 156$. In W. T. Porter's experiments a Daniell cell giving 1.1 volts was used. In the expression $Z = \frac{M}{L} I$ the value I depends upon the amperage and not upon the voltage. To compute current intensity from voltage the resistance of the circuit must be known. The resistance of the primary coil of the inductorium used by W. T. Porter is 0.73 ohm. This gives a value of I for his experiments of 1.51, which, corrected for core magnetization,[2] becomes 2.04, and a value of Z, corresponding with 250 Kronecker units, of 318. This value agrees rather well with the approximate threshold of 280 units reported by us in a previous paragraph and justifies us in concluding tentatively that to obtain pressor reflexes, stimuli well in excess of 250 Z units must usually be employed. This value, moreover, represents the *threshold* only; the marked rises of pressure reported by W. T. Porter required stimuli eight to ten times as strong as these.

We have reported in an earlier paragraph (p. 215) that blood pressure may be modified reflexly, in animals anaesthetized without drugs, by means of stimulations of less than 10 units, and, further, that even so profound an anaesthetic as urethane affects the threshold relatively little. To obtain pressor effects, stimuli 20 to 200 times as strong as these are constantly used. When we recall that well-marked reflexes of skeletal muscle are evoked with even greater ease than are blood-pressure drops, and that in an uncurarized animal such stimuli as are used for obtaining pressor effects would usually bring about marked convulsions, we may justly inquire whether the stimuli which produce a fall of pressure are not more "normal" to the organism in its ordinary life than are those which elicit a rise.

[1] Martin: This journal, 1908, xxii, p. 63 *et seq.*

[2] Martin: Measurement of induction shocks, p. 46.

The Relations of Pain Sensations to Threshold Stimulation. — Some further comparisons may be of service in deciding our point. Howell [1] states that artificial stimuli applied to naked nerves arouse sensations of pain with especial ease. Martin, E. L. Porter, and Nice [2] have made some observations on the pain threshold in human subjects. Their results were obtained by means of needle electrodes thrust through the skin, and probably represent higher thresholds than would be had from electrodes applied directly to nerve trunks. Their thresholds are expressed in β units.[3] To make them comparable with the values used in this study we have had reference to the original protocols of the experiments from which these authors drew their data and find that the thresholds for painful stimulation in their experiments have in Z units an average value of 46. Unless we choose to assume that the pain threshold in such animals as the cat is much higher than in man we must recognize that stimuli which would be sufficient to cause pain in a conscious animal may elicit typically pressure-drop instead of pressure-rise; also that the pain threshold is exceeded several hundred per cent before pressor effects become manifest, and many-fold in those experiments in which marked rises of pressure are evoked.

A pertinent inquiry in this connection is as to the quantitative relation borne by *intense* pain to the pain threshold. Obviously there are innumerable degrees of intense pain, and a wholly satisfactory criterion of any of these degrees cannot readily be established. We have made some observations, however, which seem to bear on the general problem of the relation of pain to blood-pressure reflexes. We aroused painful sensations in human subjects by the method of Martin, E. L. Porter, and Nice (*loc. cit.*); namely, with needle electrodes inserted longitudinally beneath the outer layers of skin. Our thresholds for pain sensation agreed satisfactorily with those reported by

[1] Howell: Text Book of Physiology, 5th Edition, Philadelphia, 1913, p. 280.

[2] Martin, Porter, E. L., and Nice: Psychological review, 1913, xx, p. 194.

[3] Martin: The measurement of induction shocks, p. 76.

them, averaging about 50 Z units. We find that as the strength of stimulation is increased above the threshold the painful sensations promptly take on a decidedly disagreeable character, and by the time the stimuli reach a value equivalent to five times the threshold, they are so intense that the subjects characterize their sensations as "severe" pain. They state, moreover, that were voluntary inhibition not employed, vigorous efforts to escape the pain would doubtless be resorted to.

If a five-fold multiplication of sensory stimulation above the threshold is so markedly painful even when narrowly localized, as in the method used in these experiments, surely a similar multiplication, extended over so wide a field as is represented by the sensory distribution of a great nerve trunk like the sciatic or radial, might, with justice, be supposed to be sufficient to evoke in conscious animals painful sensations much more pronounced and efforts at escape even much more strenuous,

Yet to elicit pressor responses reflexly, stimuli 20 to 200 times the threshold, as established by lowering of blood pressure, are commonly used.

The Influence of Curare.—There is in this connection another point to be considered. Blood-pressure experiments are ordinarily performed on curarized animals. The argument may be advanced that curare modifies the mechanism for regulating blood pressure so profoundly that stimuli, which in normal animals would be vastly supra-physiological, become in curarized ones wholly physiological. Some such suggestion has even been made by Hunt [1] to account for certain of his phenomena.

If curare has this effect, its use in connection with attempts to analyze the normal functioning of the vasomotor mechanism seems to us to be wholly unjustifiable and views which depend upon experiments involving its use to require re-examination. If curare is without such a modifying function, its use is attended with a danger suggested by the facts brought out in this paper, that unless stimuli of known intensity are used, they may become supra-physiological without any adequate indication of their excessive intensity being afforded. Studies now in progress

[1] HUNT: *Loc. cit.*, pp. 386 and 405.

in this laboratory are designed to establish definitely the influence of curare on the vasomotor mechanism.

However the alternatives suggested above may ultimately be resolved, the fact that sensory stimuli of physiological intensity cause reflex fall of blood pressure rather than reflex rise, seems to us fully established.

Pressor Responses to Mechanical Stimulation.—An observation frequently made, which might seem, at first glance, to contradict our contention that weak stimuli are typically depressor, is that traction on a sensory nerve, or tying or cutting such a nerve, ordinarily evokes a *rise* of blood pressure. A study of these means of stimulation, in comparison with well-known experiences of conscious human beings, suffices to show that they rank among the most painful to which the organism is liable.

Thus, tying or cutting a sensory nerve must be equivalent in immediate if not in subsequent effect to flaying the entire surface to which the nerve is distributed. That traction on a sensory nerve is exquisitely painful is evidenced from the sensations accompanying the extraction of a tooth or the removal from a pulp cavity of a "devitalized" nerve. Moreover, in many classical examples of extreme pain, such as the climax of parturition, the stimulation arises from stretching of sensitive regions. In the face of these comparisons one can scarcely maintain that the pressor responses evoked by the manipulation of sensory nerve trunks are the results of weak stimulation.

Pressor Phenomena in Normal, Conscious Organisms. — If the view is to be accepted that only excessive stimulations produce reflex pressor responses, how is the well-known fact of frequent blood-pressure rise in the normal organism to be explained? To our minds the rational explanation is to be found in the influence of psychic states upon the vasomotor mechanism. The existence of such influence is undoubted. Cyon[1] in 1869 believed it to be an essential feature of the pressure-controlling apparatus.

Since, in the conscious organism, vigorous psychic reactions may be easily aroused by relatively feeble stimulations, a fully

[1] Cyon: Comptes rendus de l'Académie des Sciences de Paris, 1869; also gesammelte Abhandlungen, 1888, p. 95.

adequate means is furnished for bringing about that rise of blood pressure which seems to be so important a part of the protective response as a whole, without the necessity of considering reflexes as the sole actuating mechanism. Meanwhile, those sensory stimuli which do not arouse fright, anger, or other psychic states inciting high pressure may be of service by inducing peripheral vaso-dilation with its accompanying improvement in peripheral circulation.

Summary

1. Reflex drop of blood pressure is the typical response in cats to sensory stimulation when the intensity of the stimulation is of the order of magnitude represented by the threshold for a spinal reflex of skeletal muscle. In cats rendered unconscious by decerebration, brain pithing, or brain compression the average threshold for reflex pressure-drop in our experiments was 8.7 Z units, as compared with a threshold of 5.2 units for the flexion reflex (E. L. Porter).

2. No difference in effect on blood-pressure was observed when different sensory nerves were stimulated. Radial, ulnar, median, sciatic, and saphenous nerves all gave pressure-drop under stimulation near the threshold.

3. Anaesthetization with ether or urethane has relatively slight effect on the threshold for pressure-drop. With ether anaesthesia this threshold averaged 14.7; with urethane anaesthesia, 15.3.

4. The threshold for reflex rise of blood pressure appears to exceed 250 Z units. In ordinary experiments on blood-pressure reflexes, stimulations ranging from this value to 2000 units are commonly used. These stimuli are from 20 to 200 times the threshold for reflex blood pressure-drop.

5. Authority is cited for the view that pain sensations are aroused with great readiness when stimuli are applied directly to sensory nerve trunks.

A study of pain sensations in human beings indicates that stimuli five times the threshold are severely painful and would surely elicit in a conscious organism most vigorous efforts to escape them. The conclusion is drawn that direct application to nerve trunks of stimuli 20 to 200 times the threshold, rep-

resents a degree of pain beyond any save possibly the most exceptional experiences of organisms, and therefore is to be considered supra-physiological.

6. The generally accepted doctrine that pressor responses are the normal results of sensory stimulation rests, as shown above, on experiments with supra-physiological stimuli and is, therefore, not justified.

7. The pressor responses which conscious organisms frequently exhibit are probably due to influences upon the vaso-motor mechanism of the psychic states induced by the stimulation, rather than to direct action of the stimuli themselves.

Sensory stimuli which do not arouse fear, anger, or other pressor-inciting psychic states probably bring about reflex peripheral vaso-dilation with a fall in general blood pressure.

A STUDY OF THE ANATOMY AND THE VASO-MOTOR PHENOMENA OF THE SYMPATHETIC NERVOUS SYSTEM IN THE TURTLE

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I. Introduction

THE sympathetic nervous system in birds and mammals has been shown to conform to a common plan of structural arrangement and, considered in the light of its physiology, there is in the different representatives of these orders an evident similarity in the character, the degree, and the number of functions innervated by it.

The anatomy and the physiology of the sympathetic system have been far less carefully investigated in the lower vertebrates, i.e., reptiles, amphibians, fishes, and cyclostomes, than in either birds or mammals, with the possible exception of the amphibians. In development the reptiles show a more highly differentiated sympathetic than any other of these lower groups. If one reasons from analogy, therefore the reptilian system would be expected to afford the best field for a study of the functions of the sympathetic of any of these lower vertebrates, since the most fruitful results have been obtained from birds and mammals, which possess a highly specialized system.

As a matter of fact, the frog has been the most studied of any form in the lower vertebrate groups. It seems wise, therefore, to state briefly the results of some observers working with this form, in view of the possible bearing of such knowledge upon the present work.

Ellis [1] in some early experiments, making use of the plethysmographic method, got results which led him to conclude that

[1] Ellis: Journal of physiology, 1885, vi, p. 455.

a vasomotor mechanism exists in the frog, and in discussing the nature of these results he states that such a mechanism is not so active in cold-blooded as in warm-blooded animals. Waters [1] was the first to describe in the frog a vasomotor effect exercised by certain of the spinal nerves upon the blood vessels in parts of the alimentary canal. In a more recent work, Langley and Orbeli [2] call attention to the occurrence in the frog of vasoconstriction upon stimulation of certain parts of the sympathetic. Their results were so exact in character as to permit a definition of the control exercised over this phenomena by different roots, rami and spinal nerves. These authors state that a comparison of the sympathetic of the frog with that of a mammal shows structural differences as to details but in general many points of similarity.

In consideration of the results obtained with the frog, on the one hand, and the high degree of differentiation both in structure and function shown by the mammalian sympathetic on the other, it seems obviously desirable to determine in how far the sympathetic system of the turtle agrees in its morphological arrangement with the phylogenetic position of the animal, and furthermore, in the study of a single function such as vasomotor action, to observe whether or not the sympathetic exercises a degree of control which can be taken to indicate a functional specialization corresponding to the relative position of the turtle in the vertebrate scale.

This work is partly a consideration of the anatomical relationship of certain parts of the sympathetic nervous system in a few closely related species of turtles and partly the presentation of the results of experiments performed with a view to determine the character and degree of control exercised by this system over the blood vessels.

II. Anatomical

Historical. — The literature bearing upon the anatomy of the turtle's sympathetic is not very extensive. This is particu-

[1] Waters: Journal of physiology, 1885, vi, p. 460.

[2] Langley and Orbeli: Journal of physiology, 1910, xli, p. 460.

larly true as regards that part of the system occurring in the trunk cavity, or the part that I shall term the abdominal sympathetic.

Bronn,[1] giving the classification of Bojanus, distinguishes seven different plexuses, but he does not make clear their point of origin from the main trunk of the sympathetic and is equally vague in the matter of the distribution of the different tracts. The names given suggest the following distribution:

Plexus cardiacus	the heart
" *aortae sinistrae*	left aorta
" *coeliacus*	coeliac artery
" *aortae descendens*	dorsal aorta
" *renalis*	kidneys
" *arteriae hypogastricae*	hypogastric artery
" *sacralis*	sciatic plexus

Owen[2] quoting Bojanus is a little more clear upon the matter, for he describes "filaments distributed from the middle cervical ganglion to the aorta, the cardiac plexus, and the coeliac plexus" and, further down towards the middle of the back, "a third ganglion which furnishes the splanchnic nerve." In regard to the termination of this system in the sacral region he adds that "the sympathetic gives off a great number of branches the divisions of which form the renal, hypogastric, and sacral plexuses." The sympathetic in the trunk cavity of Emys europea is described by Owen as a pair of cords connecting the ganglia with each other — both passing ventral to the ribs, and in place of the semilunar ganglia of mammals there are two plexuses: a smaller that sends filaments along the coeliac artery to the stomach, and a larger that sends its fibres along the mesenteric artery to the intestines. Martin and Moale[3] state that there are in the region of the third and fourth ribs and fourth spinal nerve, three branches which pass to the lungs, and in the region of the fifth and sixth spinal nerves two other branches

[1] Bronn's: Klassen und Ordnungen des Thier-Reichs, 1879, Reptilien, p. 151.

[2] Owen: Comparative Anatomy, 1866, i, p. 323.

[3] Martin and Moale: How to Dissect a Chelonian, 1881, p. 87.

from the main trunk of the sympathetic that are distributed to the kidneys and genital organs.

The early studies upon the innervation of the heart in the turtle brought forth accounts of the cervical sympathetic that are very definite in character. But with the increasing definiteness in the description there are points of diversity of opinion as to the origin and connection of the fibres which this system gives off. I do not propose to discuss at any length the cervical sympathetic, because it is not especially involved in the objects of this study; but it seems wise in passing to note a few facts, in regard to this system, that have been made clear from the study of a number of different species. According to Gaskell and Gadow [1] in Testudo gracea the third cervical ganglion may be entirely absent, having probably fused with the second. They state that in some cases all three ganglia are united into one large ganglionic mass, and they propose to call this the ganglion cardiacum basale, although the structure is suggestive of the typical ganglion fusiforme of mammals. Martin and Moale [2] on the other hand describe the third and fourth ganglia under separate names and in distinct positions, and they claim that a small nerve is given off from the fourth ganglion to the musculature of the lung. Mills [3] claims from the study of a great number of specimens, mostly of the species Pseudemys rugosa, that there is never "entire absence of these ganglia (i.e., the third and fourth), but they present every variety in size and shape and may either of them be so small as to be mere swellings on the main nerve stem." He holds to the designation of the fourth ganglion, as the G. cardiacum basale, and also claims that this structure generally gives off a strong branch to the heart. Bottazzi [4] and also Oinuma [5] have described nerve connections to the heart from the inferior cervical ganglion.

The forms studied in this portion of the work were, Chrysemys picta (Hernn), Pseudemys rugosa (Shaw), Chelopus guttatus

[1] Gaskell and Gadow: Journal of physiology, 1884, v, p. 366.
[2] Martin and Moale: *loc. cit.*
[3] Mills: Journal of physiology, 1885, vi, p. 265.
[4] Bottazzi: Archives italiennes de biologie, 1900, xxxvi, p. 18.
[5] Oinuma: Archiv für die gesammte Physiologie, 1910, cxxxiii, p. 505.

(Schnei), Chelydra serpentina, and Aspidonectes ferox. The dissections were made in most cases under a dissecting lens, and to aid in tracing the course of the fibres a saturated solution of hot corrosive sublimate or alcohol was found of great service in differentiating them from the surrounding tissue. The intra vitam method with methylene blue was used in a number of cases, but in the main did not aid materially in the work. In some cases where fine branches were given off from the ganglia this method gave results, but in the main it is better adapted to the study of nerve terminals and does not appear to be especially serviceable in differentiating sympathetic trunks.

The cervical sympathetic. — The study of this part of the sympathetic was concerned with the question of the mode of occurrence of the three posterior cervical ganglia and their immediate connections. Is there an evident tendency in any single species or throughout the different species for these ganglia to occur as a fused mass or are they recognizable as distinct bodies? What are the connections from these ganglia that appear to be common characteristics?

A comparison of the plan of arrangement of the posterior cervical sympathetic in the five species examined supports the view of a separate existence of the second, third and fourth ganglia.

The location of the fourth ganglion is close to the tenth spinal nerve and from it connecting fibres are given off to this spinal nerve and to the brachial plexus, while a single branch extends posteriorly across the neck of the first rib to unite with the ganglion of the abdominal chain. A small degree of fusion between this ganglion and the inferior cervical ganglion is occasionally shown, but it appears that this condition is the exception rather than the rule. This ganglion shows a likeness to the stellate ganglion of higher vertebrates in two respects: namely, its position with respect to the brachial plexus and the spinal nerves, and its connection with the main sympathetic trunk and the tenth spinal nerve. I am, therefore, of the opinion that it should be termed the stellate ganglion, notwithstanding the objection raised to this designation on the ground that the name carries a form distinction which is often not present.

The third or inferior cervical ganglion is usually located close to the crossing of the main sympathetic trunk and the ascending axillary artery. It is connected with the fourth ganglion in some cases by a trunk that courses alongside of the vertebralis communis artery, and in other cases by a pair of fibres which are separated to allow the passage of the artery. The latter condition suggests the annulus Vieussens of the mammalia. In addition to the branches that form the continuation of the sympathetic trunk in this region, the inferior cervical ganglion gives off branches to the brachial plexus, and to the heart. The latter branch I have carefully traced in C. picta and it there shows the following course: — Leaving the inferior cervical ganglion this ramus cardiacus continues at first posteriorly upon the pleural membrane; then arching ventrally it meets the vena vertebralis communis, alongside of which it follows in the direction of the heart, passing in order from the v. vertebralis communis to the v. subclavia and lastly to the v. anonyma.

The second or middle cervical ganglion is always easy to distinguish since it is ordinarily at the point where the common vago-sympathetic trunk separates into the vagus and the sympathetic. In some forms a well-marked branch is given off from this ganglion and joins the vagus posteriorly.

The arrangement of the ganglia of the posterior cervical sympathetic shows many variations, as has been stated by a number of different workers, but it should be the aim in studying this part, I believe, to seek the fundamental plan and to consider the variations as individual modifications of the common type. This I have attempted to accomplish by the study of different species and it has served to emphasize two things: first, that the underlying plan in the turtle is a separate existence of the second, third and fourth cervical ganglia; and second, that the fourth or stellate ganglion does not typically send fibres to the heart.

The abdominal sympathetic. — Under this division of the turtle's sympathetic is included that part contained in the thoracico-abdominal cavity. It comprises the main sympathetic trunk or "Grenzstrang," its central connections, the rami

communicantes; and its peripheral connections, the splanchnic fibres and the fibres to the reno-genital system.

The ganglia of the sympathetic chain are generally very small and irregularly placed; the latter condition often gives a zigzag course to the main sympathetic trunk. The customary position of the first ganglion of the chain is in the region of, and ventral to the second or the third rib. Bottazzi[1] has described the inferior cervical ganglion as the first of the chain, but it is not easy to harmonize such a view either with the position or the connections of this structure. The inferior cervical ganglion is located outside of the body cavity and the connection to the main sympathetic trunk is not directly from this ganglion but from the stellate.

Originating from the centra of the fourth to the eighth dorsal vertebræ inclusive, the retrahens capitis collique muscle spreads out as a large fan-shaped body on either side of the vertebral column and runs anteriorly in the neck region as a band of strong muscles. Located upon either side of this mass of muscular tissue is the chain of ganglia that forms the vertebral part of the sympathetic system. The first and second ganglia of the chain are not very conspicuous, since they are located between the retrahens capitis collique and the posterior sheet of the diaphragmaticus muscles.

It is difficult to generalize regarding the position of the remaining ganglia of the chain because so many variations are shown. In C. picta the third to the sixth ganglia inclusive occur close to the vertebral column and near the necks of the ribs; the rami communicantes extend anteriorly to the spinal nerves. The chain ganglia in C. guttatus and P. rugosa are all located more ventrally upon the "head-and-neck retractor" muscle, and in the latter form the arrangement is quite regular, although confused in places by the occurrence of nodes or supernumerary ganglia. In A. ferox, the chain ganglia are close to the spinal nerves, and actually sessile upon them in many cases, whereas in C. serpentina some of the ganglia are close to the spinal nerves and the others are either upon the necks of the ribs or ventral to them.

[1] Bottazzi: *loc. cit.*

The arrangement of the fibres given off from the abdominal sympathetic gives evidence in support of the view of Owen, that there are two plexuses in the turtle; a small anterior and a larger posterior one. A small group of fibres, rarely more than four bundles, originate from the sympathetic trunk in the region of the first and second vertebral ganglia; they pass ventrally across the wall of the aorta and are distributed to the anterior arteries of the group designated by Wiedersheim[1] as the coeliaco-mesenteric. This collection of nerve fibres I designate the anterior splanchnic group.

Fibres are given off from the sympathetic chain in the region of the third, the fourth, the fifth and the sixth ganglia and become somewhat grouped together as they pass ventrally on the side of the large "head-and-neck retractor" muscle. In some cases (C. picta, P. rugosa, and C. guttatus this set of nerve elements comes to a focus on the median surface of the kidney, and continuing from this centre fibres are distributed to the genital organs, the kidneys, and anteriorly along the dorsal aorta to the posterior coeliaco-mesenteric arteries. In the other cases (C. serpentina and A. ferox) this posterior group of fibres form a plexus upon the wall of the dorsal aorta, and thence connections are made to the same set of organs given above for the other species. The group of fibres that arise from the region of the third, fourth, fifth, and sixth ganglia of the sympathetic chain I designate the posterior splanchnic group.

It is not unusual in some forms to find nerve fibres from ganglia posterior to the sixth, distributed to the same region supplied by the posterior splanchnic group; these are, I believe, individual modifications of the typical arrangement. The sympathetic chain continues into the sacral region, but this part of the system was found impracticable for experimental purposes because of the location of the kidneys and their vascular connections; accordingly I have not made a study of this portion.

Discussion. — The study of the sympathetic in different species reveals interesting facts not evident in the examination

[1] Wiedersheim: Comparative Anatomy of Vertebrates, translated by Parker, 1886, p. 291.

of a single species. There is shown an arrangement into two groups of the fibres supplying the viscera and the collecting together of the fibres of the posterior splanchnic group into a centre in the region of the anterior border of the kidney: the latter divisions are, according to Kuntz,[1] the prevertebral sympathetic of the turtle.

There appears to be little reason for designating the last ganglion of the cervical sympathetic group the ganglion cardiacum basale, since it is evident that the usual arrangement is a separate existence of the second, the third, and the fourth ganglia, and with this condition prevailing it is not the last ganglion but the third or inferior cervical that gives rise to the cardiac branch. On the other hand, the close relationship with higher vertebrates shown by the position and the manner of connection between the fourth ganglion and the other structures of the sympathetic favor designating it the stellate.

The classification of the plexuses given by Bojanus agrees in part with the conditions as I have observed them, but on the whole it appears cumbersome and somewhat unnecessary. I have not found any group of fibres that could be properly termed a left aortic plexus; the nearest approach to anything of this sort is the group of fibres already referred to as the anterior splanchnic. This group of fibres passes very close to the left aorta, but instead of passing into the wall of this vessel it continues to the mesentery, where it is distributed to the smaller arteries that originate from the left aorta The designation of a coeliac plexus does not seem desirable, because the region supplied by the coeliac artery receives sympathetic fibres from the same group as the mesenteric and the gastro-epiplotic arteries, and all three vessels receive their sympathetic nerve supply by way of the bundle of fibres that I have termed the anterior splanchnic group.

I have failed to obtain evidence supporting the view of a sympathetic nerve supply to the lung. The fibres of the anterior splanchnic and also the main trunk that connects the cervical and abdominal sympathetic might easily be mistaken for fibres distributed to the lungs. The latter trunk is imbedded for

[1] Kuntz: American journal of anatomy, 1910–11, xi, p. 295.

the most of its length, and the former for a part, in the diaphragmaticus muscle, and this muscle is closely applied to the wall of the lung but there is no indication of a connection of these fibres with the lung tissue proper.

The first and second rami communicantes are very long in all cases, and those connecting with the remaining ganglia of the chain differ in length in the different species according to the general position of the chain ganglia. There is no indication of a pair of cords connecting the vertebral sympathetic ganglia, as suggested by Owen. This appearance is very often given because of the fact that a sympathetic ganglion is located posteriorly to its homologous spinal nerve and the rami communicantes may therefore run parallel to the sympathetic trunk for some distance.

III. Experimental

We are now to consider the vasomotor rôle taken by the sympathetic in the turtle. Notwithstanding the large amount of literature upon vasomotor action, little has been done to establish the exact analogy of this phenomenon throughout the vertebrate series. My attention was directed to the turtle because of its phylogenetic position, as already indicated. Very little has been written bearing directly upon vasomotor activities in the turtle and the references that are obtainable prove to be more in the nature of suggestions. Thus Bruner[1] in discussing the so-called "swell-mechanism" in reptiles, states "that among the accessory factors there is acceleration of the heart and probably also vasomotor adjustment including cephalic dilation and body constriction." Donaldson and Stevens[2] working upon the action of digitaline upon the heart state that "having thus found a decrease in the work of the heart and at the same time a marked rise in mean pressure we were compelled to infer a constriction of the arterioles." Mills,[3] in studying the question of a depressor nerve in the Chelonians, states

[1] Bruner: American journal of anatomy, 1907–8, vii, p. 109.
[2] Donaldson and Stevens: Journal of physiology, 1882–83, iv, p. 185.
[3] Mills: *loc. cit.*, p. 270.

that many nerves gave a marked rise of blood pressure from stimulation.

Methods. — The general method in use for taking the blood pressure of mammals can be applied with a few modifications to the turtle. The mercury manometer was tried in the first experiments, but the inertia of the mercury appeared too great for the comparatively low pressures normally present. All of the tracings were therefore made with a very small tambour manometer equipped with a double thickness of the thinnest rubber obtainable; such an instrument possessed just the right amount of resistance for the average pressures and responded very effectively to slight variations. Blood pressures in terms of millimetres of mercury were obtained by calibrating the tambour immediately after the completion of the tracings.

If we consider the anatomical relations of the arterial system and the comparatively sluggish character of the circulation, it would a priori seem best to select some vessel close to the heart from which to take blood pressure. Therefore, in the earlier experiments the following arteries were used with varying degrees of success; carotid, subclavian, right and left aortæ, the latter being the most satisfactory from the standpoint of accessibility and character of results.

In order to reach the abdominal sympathetic it was found desirable to trefine the carapace close to the line of fusion with the vertebral column, carefully separate the lungs from the "head and neck retractor" muscle and in this manner approach the sympathetic from the dorsal side. It will now readily be seen that if blood pressure be taken from any of the above enumerated vessels near the heart, stimulation of the sympathetic becomes a very awkward matter, since access to both dorsal and ventral sides is highly desirable and from the nature of the conditions this is practically impossible. What is desired is an artery in the abdominal region accessible from the dorsal side and equally as susceptible to slight changes in systemic pressure as arteries near the heart.

The right aorta courses in between the lungs and, passing posteriorly, joins a branch from the left aorta at about the level of the fifth vertebra. The location of this vessel is such that

it is easily accessible through the same opening made in the carapace for the exposure of the abdominal sympathetic, and a few trials of blood pressure demonstrated the feasibility of using it in the following experiments. It was ligated about three-fourths of an inch from its junction with the left aorta, and the canula was inserted into the right artery and directed distally, that is, towards the dorsal aorta. With this method of connection any vasoconstriction in the splanchnic region, which is mainly supplied by branches from the left aorta, will produce a rise in pressure in both the left and dorsal aortæ; the recorded pressure will not be essentially different from that actually existing in either of these vessels, and the figures obtained may be taken to represent the systemic pressure for this form.

Most of the experimental work was performed upon P. rugosa, and the majority of the animals used weighed approximately 800 gms. Where there was any considerable loss of blood during the operation it was found expedient to transfuse an equal amount of Ringer's fluid before beginning the experiments in which changes in blood pressue were to be studied. At the beginning of the operation a small hole was made in the skull through which all of the fore-brain was destroyed; the opening in the skull was then plugged with cotton so that very little hemorrhage would take place.

Results from the use of adrenalin. — The use of adrenalin extract in this work was primarily to ascertain whether the blood vessels in the turtle are innervated by sympathetic nerve fibres. For this purpose a solution of adrenalin chloride was used in dilutions of 1: 2000 and 1: 5000, and in quantities of 2 to 5 minims in an injection, depending upon the strength of the solution and the size of the turtle. In order that vasoconstriction, if such were possible, should be immediately manifest in the splanchnic area, the injection was made into the left carotid artery close to the aorta.

Injection of the adrenalin solution is followed immediately by a rise in blood pressure, the index to the sympathetic nervous control of the blood vessels. The vasoconstriction in this case is probably in the region of the coeliaco-mesenteric arteries, but

it is not possible to state definitely that all occurs in this region because some of the extract may find its way past these arteries and into the dorsal aorta, in which case it may then be distributed to the kidneys, the genital organs and the posterior extremities. In the tracing (Fig. 1) it will be noted that the interval between the injection of the adrenalin (indicated by the break upon the base line) and the beginning of the rise in blood pressure is actually about fifteen seconds. This short period favors the view that the vasoconstriction is in the region of the coeliaco-

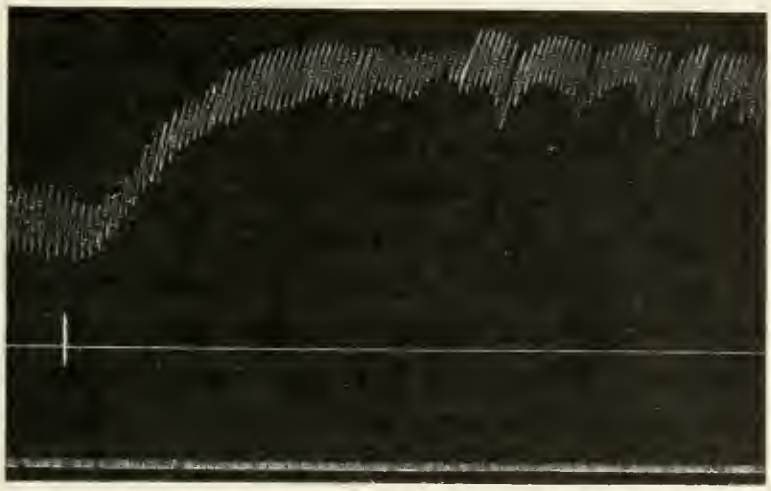


FIGURE 1. The rise in the blood pressure following an injection of a 1:2000 solution of adrenalin. Initial pressure 14 mm. Hg Maximum pressure 30 mm. Hg. Time line in seconds.

mesenteric arteries since the actual distance to this area is somewhat less than to the other possible organs. The blood pressure after the rise may be more than double the original, and the phase of maximum pressure is always several minutes in duration. A complete return to the previous pressure requires from twenty to thirty minutes, indicating that the blood vessels hold their tone for a considerable time under the influence of a small amount of adrenalin.

Two additional points are shown in the blood pressure tracings, namely, an augmentor effect upon the heart, and an interrupted heart rhythm. The former effect is so well known that mere mention of it is sufficient; the latter phenomenon, however, is not so well understood, but a discussion of it falls properly under a later division of this work.

Blood pressure and the amount of rise from vasoconstriction. — The initial mean blood pressure obtained with the turtles used in this set of experiments was between 18 and 35 mm. Hg when taken from the right aorta at the place previously indicated. Donaldson and Stevens [1] give figures for blood pressure in the terrapin which are lower than those I have obtained. Their experiments show pressures between 8 and 15 mm. Hg taken from the left aorta close to the heart. I cannot explain their results, but it is well to note that their figures when compared with those obtained in other cold-blooded animals are unusually low. Thus Schulz,[2] using the same method of determination I used, found for the frog a blood pressure of 20 to 60 mm. Hg; Hyde [3] found an average mean pressure in the skate of 20 mm. Hg; Fuchs [4] obtained pressures of 25 to 80 mm. Hg with the cephalopod; and Greene [5] records the blood pressure for the salmon as between 47 and 120 mm. Hg in the ventral aorta.

I have found a rise in systemic blood pressure from electrical stimulation of the following parts of the sympathetic system: the anterior and posterior splanchnic groups, the rami communicantes to the first and second abdominal ganglia, and the stellate ganglion. In the following table twelve different readings of blood pressure are given and the amount of rise produced by stimulation of fibres of the posterior splanchnic group.

Initial pressure in mm. Hg	*Rise from vasoconstriction in mm. Hg*
22	6
20	6
36	8
12	5
10	2
10	4
42	6
21	4
13	6
23	5
44	7
25	3

[1] Donaldson and Stevens: *loc. cit.*

[2] Schulz: Archiv für die gesammte physiologie, 1906, cxv, p. 388.

[3] Hyde: American journal of physiology, 1908–9, xxiii, p. 201.

[4] Fuchs: Archiv für die gesammte physiologie, 1895, lx, p. 189.

[5] Greene: Bulletin of the Bureau of Fisheries, 1904, xxiv, p. 437.

This particular series shows an average initial blood pressure which is a fraction over 23 mm. Hg, but this figure should not be taken to represent the average normal systemic pressure for the turtle, because in the routine experiments the loss of blood was not so carefully guarded against as when blood pressure readings alone were to be taken and therefore the figures given are generally a little lower than they otherwise would have been.

The strength of the stimulus was the same in all cases but the duration varied somewhat; the stimulation was always

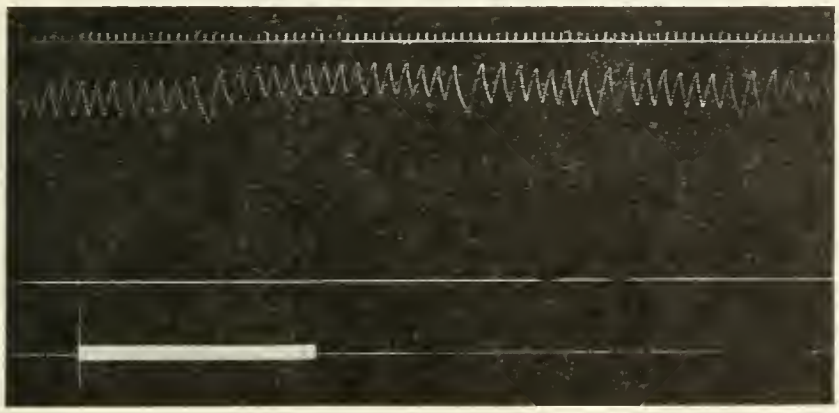


FIGURE 2. The rise in blood pressure from stimulation of the posterior splanchnic fibres. Initial pressure 32 mm. Hg. Maximum pressure 38 mm. Hg. Time line in seconds.

terminated when the maximum rise in pressure had apparently been obtained. The average rise in pressure from vasoconstriction indicated in this table is 5.2 mm. Hg. The amount of rise in blood pressure produced by direct stimulation of the splanchnic fibres is small as compared with that produced by adrenalin, but this difference is easily explained upon structural grounds. In an animal like the turtle with the splanchnic fibres so diffuse it is impossible to apply electrical stimuli effectively to more than a small part at one time, consequently the amount of rise in pressure will be proportionately small when compared to a vasoconstriction produced over the entire splanchnic area.

Results of stimulation of the posterior splanchnic group.— Stimulation of the fibres which I have designated as the posterior splanchnic group will scarcely ever fail to produce a

well-defined rise in systemic blood pressure; the result is very constant and the most satisfactory that I have obtained with any of the turtle's nerves. A record of such a rise in pressure is shown in Fig. 2. The tracing of blood pressure from stimulation of the splanchnic fibres is very different in character from that obtained with adrenalin; the beginning of the rise is never sharp and the entire phase of increasing pressure is gradual. The response to the stimulus, if the beginning of the rise in pressure be taken as the index, is generally slow to appear, the latent period varying between 5 and 15 seconds. Schaefer[1] gives the latent period as 1.5 seconds for vasoconstriction in the hind limb of the rabbit. Termination of the stimulus is not indicated by a sudden onset of fall in pressure, but, as in the increase, there is a very gradual return to the original, and unlike vasoconstriction produced with adrenalin there is very little evidence of a maintained increase in arterial tone. A rise of blood pressure of 8 mm. Hg will usually be followed by a return to normal in less than a minute after the cessation of the stimulus. It is not possible, by continued stimulation of the splanchnic, to hold the blood pressure at a higher level for a very long period; this is probably an indication of fatigue of the vasomotor mechanism.

In experiments designed to compare the vasomotor effectiveness of the right and left splanchnics the posterior group was exposed on the two sides and each was stimulated with the same strength of current — in fact from the same apparatus, since a pair of electrodes was put in position upon each splanchnic and the two pairs were connected to the opposite sides of a pole-changer. The result is very striking, since it seldom fails to show a markedly greater rise in pressure from stimulation of the right. The tracing in Fig. 3 brings out this point in a characteristic way. By carefully adjusting the strength of the stimulus, it is possible to get this phenomenon exhibited in a graduated manner. That is, with a certain strength of stimulus one obtains no change in blood pressure from stimulation of the left splanchnic and a slight increase from stimulation of the right; then by slightly increasing the strength of the stimulus a rise in pressure is obtained from stimulation of each nerve,

[1] SCHAEFER: Textbook of physiology, 1900, ii, p. 135.

but the rise is greater from stimulation of the right. The greater vasomotor effectiveness of the right splanchnic has been observed by Burton-Opitz [1] for the dog. It has long been recognized also that the right vagus in the turtle has a greater effect upon the heart than does the left. The fundamental character of the latter problem has recently been shown in the interesting observations of Garrey [2] in which he found that the right veins normally initiate the heart beat and that the vagi show a preponderant homolateral effect especially upon the basal

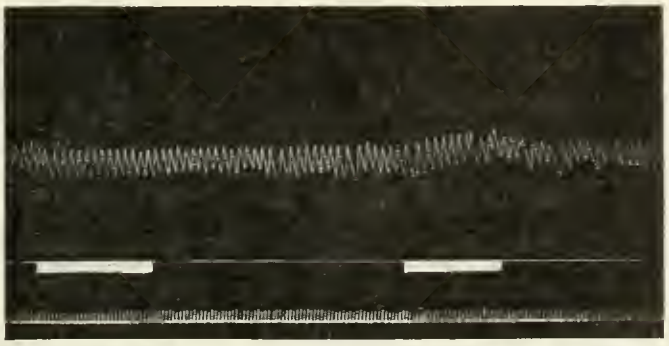


FIGURE 3. Showing the effect of a stimulus of equal intensity applied alternately to homologous fibres of the left and right posterior splanchnic groups. Signal line is the abscissa. Time line in seconds.

veins. There is, however, no suggestion in his work that could possibly be extended to include the phenomenon of vasomotor difference as here shown.

Results from stimulation of the anterior splanchnic group. — Stimulation of this group of fibres produces a small rise in blood pressure. The effects, however, as compared with those from the posterior splanchnic group, are less sure and the amount of rise in pressure is never as great from a stimulus of equal intensity. This result probaby means a smaller number of vasomotor fibres contained in the anterior tract. Langley and Orbeli [3] observed in the frog a less vasoconstrictor effect from stimulation of the second spinal nerve than from the third and fourth. If we may homologize the two cases it would appear that

[1] BURTON-OPITZ: Archiv für die gesammte physiologie, 1908, cxxiv, p. 501.

[2] GARREY: This journal, 1911, xxviii, pp. 341–48.

[3] LANGLEY and ORBELI: *loc. cit.*, p. 461.

in this species, as in the frog, the outpouring of vasomotor fibres from the main sympathetic trunk is greatest in the middle region of the trunk cavity. The experiments further show a less rapid response to a stimulus and a greater susceptibility to fatigue: toward the end of an experiment it was often observed that a perceptible rise of pressure was unobtainable, whereas a stimulation applied immediately to the posterior splanchnic would readily give a rise in pressure. The graphic record of the rise in blood pressure from stimulation of this group is essentially the same in character as that given for the posterior group.

Rhythmic fluctuations of blood pressure. — Blood pressure tracings of the turtle, at times, instead of showing a constant pressure, exhibit variations of a more or less rhythmic character; this is especially noticeable when the animal is perfectly quiet and there is a fairly rapid heart action. It was at first thought that such variations might be associated with respiration and thus be comparable to the respiratory variations of mammals, although of course of a different origin since the turtle does not possess a closed thoracic cavity. Such a view was given some weight in the work of Greene [1] upon the salmon where he shows slight variations in blood pressure and attributes them to the influence of the respiratory movements. With a possible respiratory origin in mind, simultaneous tracings of blood pressure and respiration were obtained. In order to make a tracing of respiration an opening was made in the carapace on the left side through which a small receiving tambour was applied to the surface of the lung; to this was connected a recording tambour and the latter was placed in position so that its pointer wrote directly over the record of blood pressure. In the tracing Fig. 4 the small waves in the curve of respiration indicate expiration followed immediately by inspiration; the longer pauses of variable duration indicate the interval between inspiration and expiration. The record reveals the fact that the fluctuations of blood pressure and the movements of respiration are entirely separate phenomena. Two or three respiratory movements often occur in fairly rapid succession whereas the blood pressure variations are rhythmic

[1] Greene: *loc. cit.*, p. 444.

in character and quite independent of such movements. Lingle [1] regards such blood pressure fluctuations as originating from rhythmic variations in cardiac tone and my results favor this view more than that of a peripheral origin.

In a few cases tracings have been obtained that show fluctuations in blood pressure of a different character from those described above. They are interesting because they closely simulate the "Traube-Hering" waves of mammals; one such record is shown in Fig. 5. These waves have appeared only three times in the course of the experiments, consequently my observations of them are not sufficient to justify conclusions

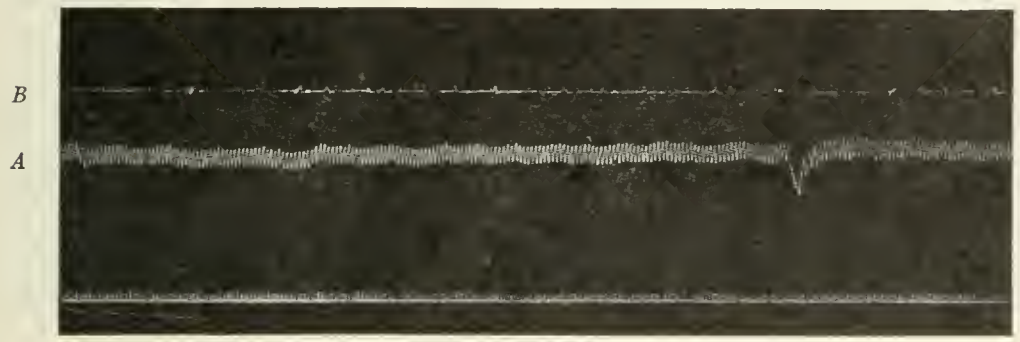


FIGURE 4. Showing (a) small fluctuations in blood pressure, and (b) the occurrence of respirations with reference to these blood pressure variations. Time line indicating seconds is also abscissa.

as to their nature. The recording of such waves in the turtle suggests a field for a comparative study of the ultimate nature of the "Traube-Hering" phenomenon.

Arhythmic character of heart action and its relation to blood pressure. — An interesting phenomenon is illustrated in the blood pressure tracings of some animals in the form of an arhythmic heart action. It appears as one long diastole followed by a short series, usually from 2 to 7, of sharp and quick systoles and intervening diastoles. The long diastole often occurs at every third or fourth short diastole and in this manner the beats may continue for several minutes. The views advanced to explain this phenomenon I shall not attempt to discuss here. I wish merely to record certain facts which seem to indicate that sudden abnormal changes in blood pressure tend to produce this

[1] LINGLE: This journal, 1905, xiv, p. 49.

condition. It is worthy of notice that Sewall and Donaldson,[1] under the designation of "dicrotism" of heart action, have described a phenomenon that is apparently the same as I have observed, and they state that this character appears upon sudden lowering of the arterial pressure by a very small amount.

Tracing *A* of Fig. 6 shows the effect upon the heart action of a sudden increase in blood pressure. At the point indicated by the asterisk, in the left hand part of the tracing, the pulmonary artery and left aorta were clamped off, whereupon blood pressure immediately rose with the resultant arhythmic character. It should be added that in this individual the trac-

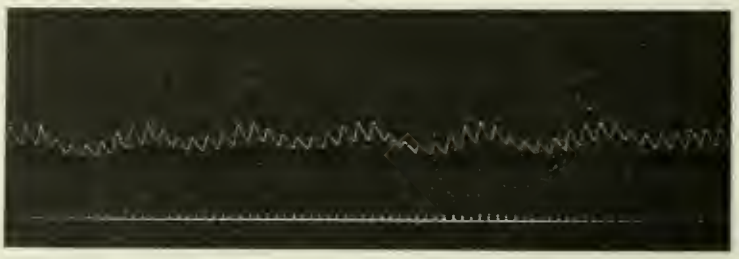


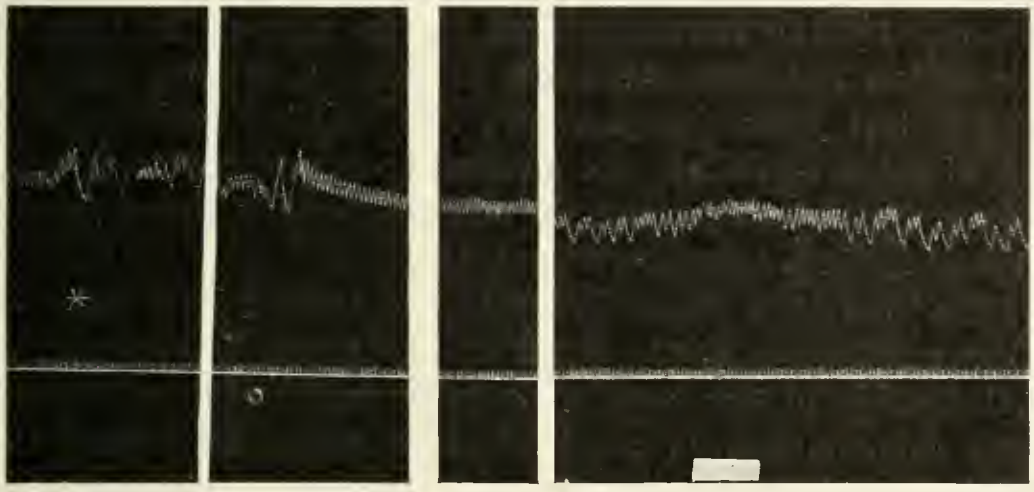
FIGURE 5. Blood pressure variations that suggest the "Traube-Hering" waves of mammals. Time line indicating seconds is also abscissa.

ing shown in the entire preceding part of the experiment was perfectly regular. In the right hand part of the tracing the clamp was removed from the artery and as the blood pressure returned to normal the arhythmic heart action disappeared. In the use of adrenalin solution the same phenomenon was evident: When the effect of the extract was at its maximum the arhythmic character appeared, and, as the constrictor action wore off and the blood pressure returned to normal, the heart regained its usual rhythm.

In tracing *B* of Fig. 6 we have a similar effect upon the action of the heart, but in this case it was produced by a lowering of the blood pressure. The right half of the tracing shows the normal rhythm in the early part of the experiment. Later on in the experiment there had been some loss of blood and probably also some loss of vascular tone; a lower blood pressure resulted and the heart showed an arhythmic action. During the

[1] SEWALL and DONALDSON: Journal of physiology, 1880–82, iii, p. 362.

interval indicated by the dash on the lower line, a stimulus was applied to the fibres of the posterior splanchnic. A vasoconstriction followed which increased the blood pressure to approximately normal and during this period the arhythmic heart action disappeared; but when the stimulus was cut off and the blood pressure fell the arhythmia appeared again. It seems evident from these results that increase in blood pressure,



A *B*

FIGURE 6. *A*, Record of arhythmic heart action following occlusion of the pulmonary artery. *B*, Record of the effect of splanchnic stimulation upon arhythmia. Time line indicating seconds is also abscissa.

such as may be produced by an occlusion of part of the arterial system or by vasoconstriction from adrenalin, and lowering of blood pressure, as produced by hemorrhage or loss of arterial tone, may both be factors in producing an arhythmic heart action.

Discussion. — The experiments outlined in the foregoing pages show that vasoconstriction can be called forth by stimulation of the sympathetic fibres supplying the splanchnic area. This result is slower than in mammals, nevertheless in a perfectly fresh turtle there are often exhibited a delicacy of response and a gradation of action that closely approximate the conditions in the mammalian mechanism. I have been able with some individuals to obtain a perceptible response, i.e., a rise in systemic blood pressure, from an effective stimulus applied for only three seconds in duration.

The observed difference in the effectiveness of the right and left splanchnic nerve groups seems especially significant in view of the fact that mammals show a similar condition. It is impossible at present to say whether the same condition prevails in the frog, for the method used by Langley and Orbeli [1] with that species consisted in observing the changes in the calibre of the small arteries under the influence of sympathetic stimulation, rather than in recording graphically the changes in blood pressure. By the former method it was possible to map out more or less definitely the origin of vasomotor fibres supplying the principal abdominal organs. The method which I have used with the turtle has not allowed an accurate determination of the comparative effects of the stimulation of different portions of the abdominal sympathetic.

Mills [2] obtained an inhibition of the heart from stimulation of the main sympathetic trunk in the upper thoracic region. A stimulation of the rami communicantes in this region with strong currents has in some instances given me results that indicate a cardiac reflex inhibition. The blood pressure tracings in these cases were very similar to those shown by Schulz [3] from stimulating the vagus in the frog. It should be further noted in this connection that reflex inhibition of both heart action and respiration have been observed in some cases from stimulation of the fibres of the posterior splanchnic group.

In a number of experiments I have tried stimulating the fourth cervical or stellate ganglion and have obtained several tracings that show a well-defined rise in blood pressure. But on the whole I have found this experiment not reliable; this may be due to a faulty technic, for the ganglion is not easy to isolate. It should be added that in all cases no change in cardiac rhythm was noticeable.

The work has furnished some evidence in favor of the view that the turtle possesses a functional arrangement that is in part similar to that in the frog, and shows a further differentiation which is suggestive of the condition found in mammals. In the turtle the group of fibres designated the anterior splanch-

[1] Langley and Orbeli: *loc. cit.* [2] Mills: *loc. cit.*, p. 254.
[3] Schulz: *loc. cit.*, p. 416.

nic gives a less marked rise in blood pressure than the posterior splanchnic group; in the frog Langley and Orbeli [1] state that the third and fourth nerves exercise the greater vasoconstriction in the mesentery and in the alimentary canal. That is, in the two animals vasomotor fibres are supplied to the splanchnic area from approximately homologous parts of the sympathetic system. There is, however, in the turtle an indication of a greater differentiation in that the fibres which exercise the maximum effect are grouped into a centre or a plexus in the region of the kidneys, a condition that suggests the mammalian arrangement.

Several experiments were made with other species of turtles, for the purpose of demonstrating whether there is a difference in vasomotor action corresponding to the difference in size and habits of such forms as C. serpentina and C. guttatus. These experiments do not indicate any characteristics that are constant for a species, but the data at hand are not sufficient to justify conclusions upon this point.

IV. Summary

1. An examination of the arrangement of the second, third, and fourth cervical ganglia in five different species of turtles confirms the view that these ganglia generally exist separately.

2. The abdominal and the cervical sympathetic systems are connected by a small trunk which extends from the fourth ganglion across the necks of the first and second ribs to the first abdominal ganglion.

3. Sympathetic fibres pass from the main sympathetic trunk to the viscera in two groups; a small anterior and a larger posterior splanchnic group.

4. A sympathetic nervous control over the blood vessels in the viscera was shown by the injection of adrenalin into the vessels supplying this area.

5. A vasoconstriction may be produced by stimulation of the fibres of the anterior splanchnic or of the posterior splanchnic group. A greater rise in blood pressure results from stimulation

[1] Langley and Orbeli: *loc. cit.*, p. 461.

of the latter group: the average rise in blood pressure thus produced was between 5 and 6 mm. Hg. The right posterior splanchnic possess a greater vasoconstricting power than the left.

6. The more common rhythmic variations in blood pressure are independent of the respiratory movements.

In conclusion it is a pleasure to acknowledge my indebtedness to Professor Frederic S. Leè and R. Burton-Opitz for valuable criticism and suggestions given during the progress of this work. I also wish to thank the authorities of the Marine Biological Laboratory of Woods Hole, Mass., for its facilities for a part of the work.

THE RELATION OF HEART ACTION TO THE RESPIRATORY METABOLISM

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THE heart, of all organs in the body, stands in closest relationship to the requirements of the tissues for energy. Dependence upon the alimentary supply of fuel is much less immediate than dependence upon the supply of oxygen; and since, in the nature of things, but little available oxygen can be stored in the living substance, the response of the heart to variations in the requirement must be immediate and, within very narrow limits of time, proportional to this requirement. In fact, if the content of oxygen in the blood on the right and left sides of the heart were perfectly constant, it would follow axiomatically that the output of blood from the heart in a unit of time would be proportional to the consumption of oxygen in the processes of metabolism. Under ordinary circumstances involving but small variations in the intensity of living, the percentage of oxygen in the blood does not change considerably; hence, under these circumstances, the volume of blood passing the heart must be at least roughly proportional to the requirements for oxygen.

If those who hold that the pulse volume or systolic output of blood from the heart is subject to but small variations are correct,[1] the number of heart beats per minute must be an index of the intensity of the oxidation taking place in the tissues. On the other hand, if the pulse volume changes under different circumstances, the intensity of the metabolism would not be indicated by the pulse rate alone, but by the product of pulse rate and pulse

[1] Cf. Y. Henderson: This journal, 1906, xvi, p. 325, and 1908–09, xxiii, p. 345.

volume, i.e., by minute volume.[1] F. G. Benedict[2] has emphasized the parallelism between the pulse rate and heat production in resting subjects. At the same time it would appear, from the determination of pulse volume in human subjects by the indirect Fick method as developed by Loewy and Schrötter[3] and by Plesch[4] and from the direct results on dogs by O. Müller and Finckh,[5] that the systolic discharge must vary considerably under different conditions of muscular activity and under the influence of baths of different temperatures. The question arises, therefore, whether the product of pulse rate by the pulse pressure, as determined by the better forms of clinical blood pressure instruments, would not give a truer index of the metabolism than pulse rate. Benedict,[6] indeed, has himself suggested that the pulse pressures should be taken into account, but has published no determinations made in metabolism studies.

It is not to be expected that this product would be closely parallel to the metabolism in different subjects, for the factor of distensibility in the arterial system of different animals is subject to wide variations.[7] Likewise, in the same animal under widely different mean pressures, one would not expect the correspondence to be very close, because the degree of distensibility is sup-

[1] According to Henderson's cardiometric results on the anaesthetized dogs with open chest, above a certain optimum rate the pulse volume diminishes very nearly in proportion to the increase in rate so that the product or minute volume does not increase as the rate increases. The variations in rate in Henderson's experiments were, however, not produced by varying the requirement for oxygen and, therefore, for blood, but by altering respiratory conditions. It is quite possible that the reaction of the heart under the two sets of conditions would be very different.

[2] Benedict, F. G.: Influence of inanition on metabolism. Carnegie Institution of Washington, Publication number 77, p. 438; also Benedict and Carpenter: Metabolism and energy transformations of healthy man during rest. *Idem*, Publication number 126, p. 135.

[3] Loewy and Schrötter: Zeitschrift für experimentelle Pathologie und Therapie, 1905, I, p. 197.

[4] Plesch: Zeitschrift für experimentelle Pathologie und Therapie, 1909, VI, p. 462.

[5] Müller, O. and Finckh, K.: *Ibid*, 1912, XI, p. 264.

[6] *Loc. cit.*

[7] Cf. Bornstein: Zeitschrift für Pathologie und Therapie, 1911, ix, p. 382.

posed to vary greatly with different mean pressures whether the mean pressure is determined by vasomotor phenomena or by the total volume of the blood. Again, the pulse pressure is certainly influenced, to some extent, by the viscosity of the blood, by the force of the systolic discharge, etc.[1] The formula of v. Recklinghausen,[2] expressing the relationship between amplitude of pulse pressure and pulse volume, is: $A = \frac{R}{\left(\frac{dI}{dp}\right)_{\mu}} \times \frac{1}{k}$, where A is amplitude or pulse pressure; R is pulse volume; the differential quantity $\left(\frac{dI}{dp}\right)_{\mu}$ denotes the relation of change in volume to change in pressure in the entire arterial system, at mean pressure (μ); and the constant k is determined by the viscosity of the blood and the diameter of the vessels. It should be noted that μ is not, itself, a factor, but simply denotes that the amplitude of the average pulse beat is a function of the distensibility of the system at the average pressure prevailing therein. Directly interpreted, the formula expresses the fact that, for any given degree of distensibility in the entire arterial system and so long as the viscosity does not change, the pulse pressure is a measure of the pulse volume.

It should be understood, then, that this inquiry is not directed to the question of whether the pulse pressure is a measure of the pulse volume (the limitations of its use are fully realized), but only to the question whether, considering these limitations, the product of average pulse pressure by the average pulse rate may not be, under certain circumstances at least, a more accurate index of the intensity of the metabolism than the pulse rate alone.

Experiments on Man. — The subjects of these experiments were second year medical students, one of the authors, and a servant in the laboratory. All of the subjects except one (E. V. A.) were men, and all but one (the woman) were in good nutritive

[1] Cf. Erlanger and Hooker: Johns Hopkins Hospital Reports, 1904, xii, p. 145.

[2] v. Recklinghausen: Archiv für experimentelle Pathologie und Pharmakologie, 1906, lvi, p. 1.

condition at the time of the experiment. None of them had any cardiac lesions. The different degrees of muscular training are indicated briefly in the table.

The experiments were conducted either in their entirety by one of the authors in person or by the medical students in the presence of one of them. All the blood pressure determinations used in the table presented herewith were made by the same observer in order to reduce to a minimum the factor of personal equation.

The plan of the experiment was very simple, namely, to determine by means of the Benedict respiration apparatus[1] the respiratory exchange in a resting or control period and then to make a similar set of observations in a period during which the energy metabolism was altered by the performance of muscular work, under the influence of cold or by the ingestion of food. The muscular work consisted in lifting a 5 kilogram weight at the rate of about one lift every four seconds. In some experiments the weight was lifted over a pulley while the subject was reclining in the usual position for a subject on this apparatus; in others the experiment was done with the subject standing, and the muscular work consisted in lifting the weight straight up and letting it down gently, while steadying the body with the other hand on the back of a chair. Especial care was taken that the nose pieces were not dislodged or loosened by the movements. Many periods had to be discarded because of uncertainty on this very important condition. Only those periods which were certainly unobjectionable as to all essential points of technique are included in the table.

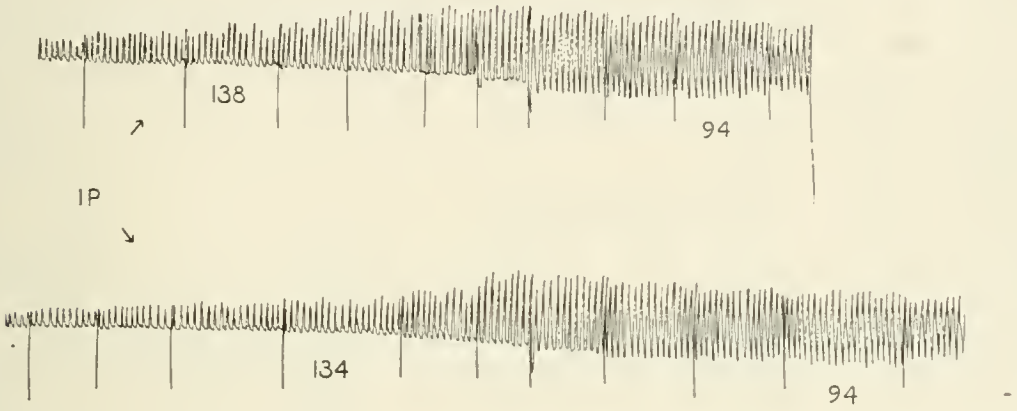
The blood pressure determinations were made by means of the Erlanger sphygmomanometer, using the criteria[2] shown in the accompanying figure.

In nearly every experimental period the pulse pressure was determined three times; first, just after throwing the valve connecting the subject with the respiratory apparatus; second, in the middle of the period, and third, just before its close. The pulse pressure, as given in the table, is the mean of these three

[1] Benedict, F. G.: This journal, 1909, xxiv, p. 345.
[2] Erlanger: This journal, Proceedings, 1908, xxi, p. xxiv.

readings. The pulse was counted at least three times in each period.

Discussion of Results. — The general table I, in which the gross results are presented, requires but little comment. As regards the blood pressure it is unfortunate that the mean pressure was not recorded for all of the subjects. Likewise in two cases the weight of the clothes was not obtained so that the net weight is not known. In one or two instances the size of the respiratory quotient is difficult to account for. Thus, in the experiment with A. S. and A. W. B., the quotient fell very noticeably when the change was made from the reclining to the stand-



ing position. The same is to be seen in certain experiments by Emmes and Riche[1] on the influence of body position on the respiratory exchange. Since special care was taken to have the mouth sealed tight, with adhesive plaster, and, in addition, the subject was cautioned repeatedly about keeping the lips tightly closed, and the nose pieces were frequently examined for their competency, it seems clear that the higher quotient is in some way associated with a change in depth of respiration or possibly with a difference in the pulmonary circulation. In several instances, also, the quotient rose distinctly in the working period as compared with the resting period immediately preceding. The subject always began to lift the weight about ten minutes before the valve was thrown connecting him with the respiration apparatus, but, apparently, this time was not in every case sufficient to establish an equilibrium between the rate of production and

[1] Emmes and Riche: This journal, 1911, xxvii, p. 406.

TABLE I

GROSS RESULTS OF EXPERIMENTS ON HUMAN SUBJECTS. ALL EXPERIMENTS TWENTY MINUTES IN DURATION

Exp. No.	Subject	Net weight kgm.	Period No.	Condition of exp.	Mean pressure	Pulse pressure	Pulse rate	Heart action PPxPR	O_2 Abs. per min. c.c.	O_2 Abs. per sq. M. per min. c.c.	CO_2 elim. per min. c.c.	R.Q.
				EFFECT OF MUSCULAR WORK								
I	J. R. G., not in muscular training	56.2	1	Standing, resting	117	26	79	2054	273	144	212	.78
			2	" working....	133	34	110	3740	418	221	334	.80
II	" "		3	Reclining	115	42	70	2940	244	129	187	.76
			4	Standing	123	36	88	3168	224	119	186	.83
			5	" , working	122	36	112	4032	416	221	353	.85
III	" "		6	Standing, resting	113	38	88	3344	257	136	215	.84
			7	" working (after lunch).....	124	35	98	3430	340	180	310	.91
IV	A. S., laboratory servant	56	1	Reclining		32	87.5	2800	261	145	246	.95
			2	"		29	80.5	2334	244	135	212	.87
			3	Standing, resting		26	98	2548	247	133	195	.79
			4	Reclining,(after lunch)		34	75	2550	231	126	197	.86
			5	Reclining, working ..		40	88.5	3540	359	199	331	.92
V	J. S. B., ball player	80.5	1	Standing, resting		25	91	2275	304	133	252	.83
			2	" working....		35	94	3290	408	178	345	.85
VI	E. M. D., sprinter		1	Standing		26	99	2574	333		265	.80
			2	" , working		34	104	3536	502		342 [1]	
VII	A. W. B., not in training but well developed		1	Reclining		33	65	2145	255		224	.88
			2	Standing		29	91	2639	284		221	.78
VIII	J. P., well developed muscularly, in moderate training	70.8	1	Standing, resting	108	24	89	2136	317	151	268	.84
			2	" working....	108	31	92	2852	409	194	328	.80

IX	E. V. A., former athlete	83.4	1	3d day fasting, reclining	112	46	75	3450	253	108	178	.70
			2	Standing (faint)		22	122	2684	270	115	187	.69
				EFFECT OF COLD BATH								
X	J. S. B.	80.5	1	Before taking bath, reclining		?	69		305	133	267	.88
			2	Just after bath 10°C., shivering		62	91	5642	714	311	580	.81
			3	Warm, resting quietly		32	80	2560	335	146	276	.86
				EFFECT OF FOOD								
XI	E. V. A., fasting	83.4	2	Standing, before eating		22	122	2684	270	115	187	.69
			3	" 2 hr. after eating beefsteak		26	146	3796	313	133	210	.67
XII	E. K.			Ate 625 gm. beefsteak,	finishing	at 12 M.						
			1	1.40 P.M., reclining	88	32	76	2432	315		275	.88
			2	2.40 P.M., reclining	85	34	73	2482	329		262	.80
			3	3.40 P.M., reclining	88	43	76.5	3289	341		272	.79
			4	4.40 P.M., reclining	90	36	76	2736	326		261	.80
			5	5.40 P.M., reclining	88	32	76	2432	332		248	.75
XIII	E. K.			Ate 312.5 gm. beefsteak and 23.5 gm. urea, finishing at 12.20 P. M.								
			1	1.20 P.M., reclining		32	77	2464	307		244	.80
			2	2.30 P.M., reclining		30	75.5	2365	293		238	.81
			3	3.30 P.M., reclining		34	72.5	2465	305		205[1]	.67
			4	4.40 P.M., reclining		32	76	2432	297		220	.75
			5	5.35 P.M., reclining		32	76	2432	312		240	.77
XIV	J. S.	53.0	1	No breakfast, reclining		25	79	1975	230	132	174	.75
			2	One hr. after eating lunch containing lactose		25	75	1875	212	122	206	.99

[1] Soda lime exhausted.

TABLE II

RELATION OF HEART ACTION TO METABOLISM IN THE HUMAN SUBJECT. COMPARISON OF TWO CRITERIA

	Subject	Period	$\frac{PP \times PR}{O_2 \text{ c.c. per min.}}$	Per cent variation	$\frac{PP \times PR}{CO_2 \text{ c.c. per min.}}$	Per cent variation	$\frac{PR}{O_2 \text{ c.c. per min.}}$	Per cent variation	$\frac{PR}{CO_2 \text{ c.c. per min.}}$	Per cent variation
					EFFECT OF MUSCULAR WORK					
I	J. R. G., not in muscular training	1	7.1		9.2		0.28		0.35	
		2	8.9	+ 25.0	11.2	+ 21.0	0.26	− 7.1	0.33	− 5.7
II		3	12.0		15.7		0.28		0.37	
		4	14.1	+ 17.0	17.0	+ 8.2	0.39	+ 39.1	0.47	+ 27.0
		5	9.6	− 25.0	11.4	− 21.0	0.27	− 3.6	0.32	− 13.5
III		6	13.0		15.6		0.34		0.41	
		7	10.0	− 23.0	11.0	− 29.5	0.29	− 14.7	0.32	− 22.0
IV	A. S., laboratory servant	1	10.7		11.3		0.33		0.35	
		2	9.6	− 10.0	11.0	− 2.6	0.33	± 0.0	0.38	+ 8.6
		3	10.3	− 3.7	13.0	+ 15.1	0.39	+ 18.2	0.50	+ 43.0
		4	11.0 [1]	− 10.0	12.9	− 17.0	0.32	− 22.0	0.38	− 29.0
		5	9.9		10.7		0.25		0.27	
V	J. S. B., ball player	1	7.4		9.0		0.30		0.35	
		2	8.0	+ 8.0	9.5	+ 5.5	0.23	− 23.0	0.28	− 20.0
VI	E. M. D., sprinter	1	7.7		9.7		0.29		0.37	
		2	7.0	− 9.0			0.21	− 28.0	0.30	− 20.0
VII	A. W. B., not in training, but well developed	1	8.4		9.5		0.25		0.28	
		2	9.3	+ 10.0	11.9	+ 25.0	0.32	+ 28.0	0.41	+ 46.0
VIII	J. P., well developed muscularly	1	6.7		8.0		0.28		0.33	
		2	7.0	+ 4.5	8.7	+ 8.7	0.22	− 21.0	0.28	− 15.1

IX	E. V. A., fasting	1	13.6		19.4		0.29		0.42	
		2	9.9	− 27.0	14.3	− 26.2	0.45	+ 55.0	0.65	+ 65.0
	Average of work experiments			14.4		14.9		21.6		25.8
	Effect of Cold Bath									
X	J. S. B.	1					0.23		0.26	
		2	7.9		9.7		0.127	− 48.0	0.156	− 40.0
		3	7.6	− 3.8	9.2	− 5.1	0.24	+ 4.3	0.31	+ 19.0
	Effect of Food									
XI	E. V. A.	2	9.9		14.3		0.45		0.65	
		3	12.1	+ 22.0	18.0	+ 25.8	0.46	+ 2.0	0.69	+ 6.2
XII	E. K.	1	7.7		8.8		0.24		0.28	
		2	7.5	− 2.6	9.4	+ 6.9	0.22	− 8.3	0.28	± 0.0
		3	9.6	+ 25.0	12.0	+ 36.3	0.22	− 8.3	0.28	± 0.0
		4	8.4	+ 9.0	10.4	+ 18.4	0.23	− 4.2	0.29	+ 3.6
		5	7.3	− 5.0	9.8	+ 11.3	0.23	− 4.2	0.31	+ 10.6
XIII	E. K.	1	8.0		10.1		0.25		0.31	
		2	8.0	± 0.0	9.9	− 2.0	0.26	+ 4.0	0.32	+ 3.2
		3	8.1	+ 1.2			0.24	− 4.0		
		4	8.2	+ 2.5	10.9	+ 8.0	0.26	+ 4.0	0.36	+ 16.0
		5	7.7	− 3.7	10.1	±0.0	0.24	− 4.0	0.32	+ 3.2
XIV	J. S.	1	8.5		11.3		0.34		0.45	
		2	8.8	+ 3.5	9.1	− 19.5	0.35	+ 2.9	0.36	− 20.0
	Average of food experiments			7.95		12.8		4.6		6.3

[1] Brackets indicate periods compared; where no brackets are used, comparison, in all cases, is with first period.

the rate of elimination of CO_2. One other high quotient, the first with A. S., a colored laboratory servant, is doubtless due to augmented breathing, the result of a little apprehension in this first experience with the respiratory apparatus. Aside from these instances, the fluctuations in the quotient are only of such size as would be expected from one period to another, taking into account the nutritive conditions. Calculated to the basis of a unit of surface area, the resting periods of the different subjects agree fairly well as to the absorption of oxygen.

Comparison of the two Criteria. — In Table II are brought together the ratios of total heart action (product of pulse pressure by pulse rate) and of pulse rate to the oxygen absorption and carbon dioxide elimination respectively. The figures, as they stand in the first column of results, denote the increase in pressure in millimetres of mercury above the diastolic pressure to which the heart must raise the arterial pressure in order to deliver each cubic centimetre of oxygen to the tissues. In the third column are corresponding figures for the removal of each cubic centimetre of carbon dioxide. The figures in columns five and seven represent the fractional part of a heart beat necessary for the same functional work. The intermediate columns contain figures representing the percentile variations which these ratios suffer in successive periods. A low percentile figure obviously denotes a close approach to parallelism between the criterion used and the metabolism in the successive periods with the same individual.

It will be readily seen that, when the metabolism is increased by muscular work, whether the work consists in merely holding the body in the erect position as contrasted with the reclining position, or consists of lifting a weight, the product of pulse pressure by pulse rate is a better index of the metabolism than is the pulse rate alone; for the ratio of total heart action (in this sense) to the oxygen absorption or carbon dioxide elimination, as the case may be, more nearly approximates a constant value for each individual.

It is worthy of note that this parallelism is more nearly perfect and the ratio is a smaller one in muscularly well developed and well trained individuals than for a person not so developed.

The lowest figures encountered are with subjects J. S. B., E. M. D., and J. P. J. S. B. was a professional base ball player who had been active the entire summer preceding the experiments, which were conducted in December, and had kept himself in good muscular tonus by gymnasium work. E. M. D. had been a sprinter on his college team and was in good muscular tonus. J. P. had kept up regular gymnasium work. E. V. A. had been a college athlete, but had not kept up regular exercises and, at the time of the experiment, had been for three days on a fasting regime. On standing perfectly still for the purpose of the experiment she felt faint, ample cause for which is found in the failure of the heart to react or, perhaps more correctly, in the failure of vasomotor tonus, which, coupled with the hydrostatic effect of the upright position, denied the heart an adequate filling.[1] *The high figure representing the ratio of heart action to oxygen absorption, therefore, denotes poor economy of heart action.* The range of this ratio is from 6.7 in J. P., a person of good muscular development and in good tonus, to 13.6 in the fasting subject. It is doubtful whether sex has anything to do with the matter.

The ratio of heart action or of pulse rate to CO_2 elimination is not so nearly constant even in muscularly well developed persons. The average percentile variation in the oxygen column is 14.4 for total heart action and 21.6 for pulse rate. In the carbon dioxide column the average for total heart action is 14.9 and for pulse rate 25.8. It will be seen later that this relationship holds for the influence of food.

Out of the six experiments where muscular work was done by lifting a weight, in five the pulse pressure was distinctly increased. The data as to the mean pressure are not complete enough to say certainly that this always signifies an increase in pulse volume; but this is altogether probable, for in the absence of a change in viscosity it would require a fall in mean pressure to give a larger pulse pressure, if the pulse volume did not increase, and in the few experiments where the mean pressure was determined it certainly did not fall. Burton-Opitz[2] has shown that an in-

[1] Cf. Erlanger and Hooker: *loc. cit.*

[2] Burton-Opitz, R.: Archiv für die gesammte Physiologie, 1908, cxix, p. 359.

crease of CO_2 in the blood produces a greater viscosity, but his results do not indicate that the small increase in CO_2 which might accompany the amount of muscular work performed in these experiments would be great enough to alter the pulse pressure materially through this means.

An even greater increase in pulse pressure is seen (Table I) in the experiment on the influence of cold, producing intense shivering. There can be no question about the pulse pressure or about the pulse rate. How much closer the metabolism follows the total heart action than the pulse rate alone is seen in Table II. This man's heart, therefore, responded to an increased requirement for oxygen produced by muscular work and by cold (largely muscular work also) in the same way. Here again the factor of viscosity may play a small, and relatively unimportant, role, for cold increases the viscosity to some extent.[1] To say that the increased pulse pressure does not denote a greater pulse volume, however, it would be necessary to suppose that the mean pressure had fallen greatly or that the viscosity had increased more than 100 per cent. The former certainly cannot be true and the latter is extremely unlikely judging by the results of Burton-Opitz on animals. Besides, the very close approach to a parallelism between total heart action and the oxygen absorption would have no meaning if it did not signify a proportionate increase in the supply of oxygen to the tissues. Both Schapels[2] and Bornstein[3] found, by gasometric methods, an increase in pulse volume as the effect of a cold bath, and Bornstein found the larger pulse volume accompanied by an increase in the pulse pressure even *with a considerable increase in mean pressure.* The opposite result, namely a lower pulse volume obtained on anaesthetized animals subjected to a cold bath, which is reported by Müller and Finckh,[4] is possibly open to the interpretation that an anaesthetized animal behaves like a cold blooded animal.

Influence of Food. — There are four experiments in this series in which the influence of food was studied. Two of them

[1] Burton-Opitz, R.: Journal of experimental medicine, 1906, viii, p. 59; also Lommel: Archiv für klinische Medizin, 1904, lxxx, p. 308.

[2] Schapels: *loc. cit.*

[3] Bornstein: *loc. cit.*

[4] Müller and Finckh: *loc. cit.*

show a marked dynamic action of the food. In the first (E. V. A.) the subject broke her fast by eating a luncheon containing, among other things, a large beefsteak. Two hours afterward the oxygen absorption showed an increase of 16 per cent. The pulse pressure had increased from 22 to 26 millimetres of mercury and the pulse rate had risen from 122 to 146, an increase of 19 per cent. The increase in metabolism is *proportional to the increase in pulse rate* rather than to the product of pulse pressure by pulse rate. (See Table II.)

In the next experiment, in which the subject ate a large meal of beefsteak and the metabolism was determined (always in the same position) at hourly intervals up to the sixth hour after completion of the meal, the mean pressure changed but slightly and the pulse is nearly uniform; but the pulse pressure rose from 32 in the first hour to 43 in the third hour after eating.

In the following experiment on the same subject, a meal containing just half as much beefsteak and an equal quantity of nitrogen in the form of urea, was eaten. Much more water, however, was taken with this meal. Whatever dynamic effect was produced was nearly uniform throughout the several periods. The metabolism was not determined previous to the meal. The urea was given for the purpose of testing the statement of N. Zuntz,[1] that the ingestion of urea increases the metabolism and is, therefore, a factor in the specific dynamic action of protein. If this were true, the dynamic effect of the meal eaten in this experiment should have been as great as that of the meal taken in the previous experiment, i.e., assuming the same basal metabolism, the oxygen absorption should have been as great. Lusk [2] has shown by means of the calorimeter that the ingestion of 12 to 17 grams of urea, given in 150 c.c. water, had no effect on the heat production of a dog of 9.3 kilos body weight.

The last experiment of the series was planned for the purpose of testing the effect of a large increase in CO_2 production on the heart action. The ingestion of a luncheon containing 100 grams lactose resulted in an increased elimination of more than 30 c.c. of CO_2 per minute, but a smaller absorption of oxygen. The

[1] N. Zuntz: Zentralblatt für Physiologie, 1909, xxiii, p. 960.
[2] Lusk, Graham: Journal of biological chemistry, 1912, xiii, p. 27.

R. Q. rose from 0.75 to 0.99. The pulse pressure was the same as before eating, but the pulse rate had fallen. This shows clearly, as intimated on page 263, that the pulse rate follows the O_2 absorption rather than the CO_2 production.

Taking all of the experiments with food together, it is clear that the small variations in metabolism here produced are not accompanied by proportional variations in the total heart action, except as that is determined by the pulse rate. But for the single high pulse pressure in the third period, Experiment XII (see Table II), the ratio between total heart action and oxygen absorption would be the same as between the pulse rate and oxygen absorption (see average percentile variations). The slightly higher pulse pressures usually observed after eating meat are not due, therefore, to anything done in the service of a larger blood supply, but may be explained, in part at least, by a greater viscosity of the blood. Burton-Opitz[1] has found the viscosity after meat feeding in dogs very much higher than after inanition, or after exclusive carbohydrate or fat feeding. Experiments of the sort reported here, particularly with carbohydrate food such as dextrose, should be repeated in view of the effects on the volume of the circulating fluid observed with this foodstuff by Fisher and Wishart.[2]

Experiments on Anaesthetized Dogs. — Two series of experiments were performed on anaesthetized animals. In both, the respiratory metabolism was determined by connecting the trachea directly to the Benedict respiration apparatus and conducting the experiment in all essential respects just as in the use of this apparatus with human subjects. In series A the blood pressure from the carotid was recorded continuously on a Brodie kymograph by means of a Hürthle manometer, the manometer being calibrated on each record against a mercury manometer. This series of experiments was reported in preliminary form two years ago.[3] Realizing the defects of the Hürthle manometer as a means of recording the pulse pressures, as pointed out by Porter,[4]

[1] Burton-Opitz: Archiv für die gesammte Physiologie, 1900, lxxxii, p. 447.

[2] Fisher and Wishart: Journal of biological chemistry, 1912, xiii, p. 49.

[3] This journal, Proceedings, 1911, xxvii, p. xviii.

[4] Porter: Journal of physiology, 1892, xiii, p. 573.

Frank,[1] and Wiggers,[2] the detailed report has been delayed until an opportunity should offer to confirm the general results by means of the optical manometer of Frank. Through the kindness of Dr. C. J. Wiggers, of this laboratory, such an opportunity occurred recently and, in conjunction with Dr. Wiggers, a second series (B of the table) has been carried out. The blood pressure was not recorded continuously, but tracings were taken every ten minutes (sometimes oftener) throughout the experimental period. It is gratifying to find that the *variations* in pulse pressure from one period to another in the earlier series were entirely trustworthy for the purpose in hand.

There are certain obvious advantages in working in this way with anaesthetized animals: (1) The blood pressure determinations can be made with greater accuracy. (2) By analysis of the arterial and venous blood drawn simultaneously from the left and right sides of the heart and by dividing the percentage difference in oxygen in the two samples into the total oxygen absorption, the minute volume can be determined. The pulse volume is found by dividing minute volume by pulse rate. (3) The respiratory quotient can be checked by these blood analyses. There are, however, certain special conditions, the bearing of which it will be well to emphasize here for the benefit of any one who may wish to repeat the experiments, or combine the estimation of respiratory exchange on anaesthetized animals with any other form of experiment.

1. Influence of Opening the Chest on Respiratory Exchange. — In a considerable number of experiments an attempt was made to determine the volume of blood flow by the cardiometric method, using a glass plethysmograph similar to the one first employed by François-Franck and more recently by Lehndorff.[3] This method was soon abandoned because it was found that with the chest open the respiratory exchange through the trachea was greatly altered. Two experiments (Nos. 2 and 3)

[1] Frank: Zeitschrift für Biologie, 1903, xliv, p. 445; 1905, xlvi, p. 512; 1908, i, p. 309.

[2] Wiggers: This journal, 1912, xxx, p. 233.

[3] Lehndorff: Archiv für experimentelle Pathologie und Pharmakologie, 1909, lxi, p. 418.

which illustrate this fact are included in Table III. In both, the absorption of oxygen and the elimination of carbon dioxide are considerably reduced in the open chest period. The only cause for this is the exchange of gases which can readily take place between the blood and the extrapulmonary air. Should this extrapulmonary exchange be equal as regards the two gases, the respiratory quotient would not be affected (Experiment 2); but if it should be unequal and if the intrapulmonary absorption of oxygen should be reduced more than the intrapulmonary elimination of carbon dioxide, the R. Q. would be increased (Experiment 3). In a number of experiments which have been discarded the opposite conditions prevailed, producing a very low R. Q. In short, the intrapulmonary exchange with the chest open is altogether unreliable. A single illustration will suffice. Dog XXIII, anaesthetized with chloretone and morphine, gave, with open chest, in a certain period, a respiratory quotient of 0.56. Analysis of blood[1] drawn simultaneously from the right heart, by a sound introduced through the jugular vein, and from the carotid artery at the beginning and end of the period resulted as follows (all numbers express percentage by volume):

	Arterial		*Venous*	
	O_2	CO_2	O_2	CO_2
Beginning	5.42	51.05	2.55	61.27
End	16.1	42.81	2.85	59.58

It is evident, from the respiratory quotient, that more oxygen was absorbed through the trachea, in proportion to the amount of carbon dioxide eliminated by this route, than should have been. There is no known form of combustion in the animal body which would yield a quotient of .56. And yet, at the end of the period, the blood was losing more carbon dioxide than at the beginning. The conclusion is inevitable, that some carbon dioxide was being lost directly to the extrapulmonary air. In spite of this the mean pressure remained high (110) to the end of the period.

[1] By method of HALDANE. All analyses reported in this paper have been made by the same method, using the apparatus devised by BRODIE. HALDANE: Journal of physiology, 1897–98, xxii, p. 465. HALDANE and BANCROFT: *ibid.*, 1902, xxxii, p. 232; BRODIE: *ibid.*, 1910, xxxix, p. 391.

Using Henderson's interpretation, this may mean only that the carbon dioxide had not yet fallen far enough to produce a loss of vasomotor tonus. The heart rate, however, was very rapid (165) and the minute volume very small (724 c.c.).

2. Influence of Artificial Respiration. — For the open chest experiments a special form of artificial respiration had to be devised, permitting the measurement of the oxygen absorption and the carbon dioxide elimination. Since this method proved, after a time, to be quite successful and since it can be readily adapted to the purposes of the administration of oxygen or of resuscitation, making the Benedict apparatus a sort of pulmotor, it will be given a separate description.

The importance of so regulating any form of artificial respiration that the carbon dioxide of the blood will be carried away no faster than it is formed has been emphasized by Henderson[1] in connection with his acapnia theory of shock. The experience gained in this series of experiments has led the authors to agree with Henderson entirely as to the importance of this factor — not so much in relation to what is technically known as "shock," but especially in relation to the measurement of the respiratory exchange. When one attempts to replace a physiological mechanism, as nicely adjusted to respond to any slight variation in the blood gases as the respiratory centre is, with an artificial mechanism which takes no reckoning of the condition of the blood gases, very great discrepancies are found in the respiratory quotients. It is only by analysis of the blood at the beginning and end of the metabolism period that one can tell whether the ventilation of the lungs has been of appropriate strength to maintain the blood gases at their proper levels, and if they have not been so maintained, the exchange as measured may be worthless as an index of what goes on in the tissues. Naturally it is on the carbon dioxide determination that the greatest error is likely to fall, because all the fluids of the body are saturated with carbon dioxide and a great deal is stored in these fluids normally at all times. When the blood loses carbon dioxide, therefore, the tissues immediately begin to release it and a considerable depletion may occur before the blood shows a great change.

[1] Henderson, Y.: This journal, 1908, xxi, p. 126.

TABLE III

GROSS RESULTS OF EXPERIMENTS ON ANAESTHETIZED DOGS

Exp. No.	Dog No.	Weight kgm.	Surface sq. m.	Length of period	Average body temp. °C.	Heart action				Respiratory metabolism			
						Average mean P.	Average pulse P.	Average pulse R.	PPxPR	O_2 per min. c.c.	O_2 Per sq. M. per min.	CO_2 per min. c.c.	R. Q.
					SERIES A								
1	XXV	17.0	0.752	40 min.	36.5	125	81	84	6808	122	162	105	.86
				42 min.	37.0	126	85	72	6542	126	168	103	.81
2	XXVI	10.7	0.543	1 hr.	35.5	153	28	168	4374	87.3	161	73.2	.84
	Open chest			40 min.	35.4	120	42	230	9660	77.2	142	64.9	.84
3	XXVII	23.0	0.906	30 min.	38.0	131	38	75	2892	141	155	117	.83
				30 min.	38.0	137	44	81	3560	156	172	129	.82
	Open chest			20 min.	38.0	140	36	222	7986	86.4	95	83.7	.97
4	XXVIII	16.6	0.725	30 min.	36.0	136	26	115	2950	107	147	91	.85
	Artificial resp. chest			1 hr.	36.0	134	20	177	3534	116	160	90	.78
5	XXXII	9.4	0.498	40 min.	38.3	84	22	169	3718	86	172	67.7	.79
	Artificial resp., chest closed			2 hr.	39.0	51	34	202	6868	95.5	191	73.1	.77
6	XXXIII	12.5	0.603	30 min.	38.5	101	50	118	5900	141.4	234	131.1	.93
				1 hr.	39.0	99	43	132	5676	153.5	254	129.6	.84
7	XXXV	10.6	0.540	2 h. 14 m.	37.5	104	62	130	8120	77.8	144	63.8	.82

8	XXXVI	30.0	1.080	2 hr.	38.0	90	27	148	4440	242	224	189	.80
				38 min.	38.0	108	30	168	5040	274	253	195	.71
9	XXXVIII	10.8	0.547	2 h. 2 m.	36.8	96	33	150	4950	70.1	128	58.3	.83
				1 hr.	36.5	115	28	174	4872	79.6	146	58.0	.73
	SERIES B												
10	XL	13.1	0.617	1 hr.		60	38.9	142	5485	81.6	132	61.5	.75
				1 hr.		58	32.3	122	3942	63.2	102	50.5	.79
11	XLI	7.01	0.386	1 hr.		36	32.4	118	3823	38.6	100	29.7	.77
12	XLII	9.2	0.491	1 hr.		59	52.1	122	6365	50.9	103	50.5	.99
				1 hr.		53	53.4	119	6330	45.0	92	35.6	.79
13	XLIII	10.2	0.526	1 hr.	37.2	72	40.4	149	6018	61.7	117	58.3	.95
				1 hr.	37.0	66	35.8	192	6848	72.4	138	60.4	.83
	After 100 c.c. blood drawn			1 hr.	37.0	41	28	206	5768	63.6	120	60.4	.95
14	XLIV	14.9	0.678	1 hr.	36.0	92	36.2	154	5569	84.4	124	73.8	.87
				1 hr.	36.3	99	32.7	165	5397	86.0	127	76.3	.88
	After 305 c.c. blood drawn			1 hr.	36.8	56	24.4	195	4770	87.0	132	71.1	.82
15	XLV	13.5	0.635	1 hr.	35.5	64	24.3	128	3110	75.5	119	67.4	.89
	Muscle stimulated.			1 hr.	35.5	61	23.7	138	3294	87.7	138	74.2	.84
	After 250 gm. blood drawn			1 hr.	36.0	48	18.1	163	2956	86.6	136	80.2	.92

When an animal was deeply narcotized, particularly with morphine, and the respiration had become too slow to supply the requisite amount of oxygen, it was the custom, early in this work, to resort to the artificial scheme even with the closed chest. The danger of overventilation is illustrated in the case of Dog XXXV, which is No. 7 of Table III. The respiratory quotient in the first period was 0.76[1]; in the second period it was 0.82. Blood gas analyses from samples drawn at the beginning and end of the second period were as follows:

	Arterial		*Venous*	
	O_2	CO_2	O_2	CO_2
Beginning	19.67	50.48	12.50	54.93
End	20.68	47.01	11.23	55.94

Clearly the cause of the higher R. Q. in the second period lies in the fact that, during the period, the store of carbon dioxide in the blood, though not yet in the tissues, was being gradually reduced. The oxygen in the arterial blood had increased by one per cent, showing, also, that the artificial respiration had been stronger than necessary.

3. Influence of the Depth of Anaesthesia. — The depth of anaesthesia has much to do with the uniformity of the respiratory quotients. Reflex stimulation of the respiratory centre from the wound in the neck will cause a pumping out of carbon dioxide in the same manner as overventilation by artificial means. The result is a quotient that is too high for the metabolism known to be taking place in the animal. Then if more anaesthetic should be given in the attempt to control the respiration, the result often is an ensuing period of profound narcosis, in which there is a compensating increase in the carbon dioxide, causing a quotient that is too low. Analyses of the arterial blood at the beginning and end of the second period with Dog XIII (No. 12 in Table III) prove that this is the cause of the low quotient in the period shown.[2]

[1] This period is not reported in the table because clots had interfered with the blood pressure record.

[2] See also in this connection recent experiments on the influence of ligation of the abdominal vessels on the respiratory quotient. Murlin, Edelmann, and Kramer: Journal of biological chemistry, 1913, xvi, p. 79.

	Arterial	
	O_2	CO_2
Beginning of Period II	15.53	35.30
End of Period II	18.57	42.20

In a previous period, which preceded this one by an interval of only 20 minutes, the R. Q. was .99. The low percentage of carbon dioxide in the blood is thereby explained. The same explanation applies to all the very high quotients shown in the table. The exaggerated respiratory activity which was responsible for the high quotients in experiments 13 and 15 was due to hemorrhage.

The anaesthetic used throughout was chloretone. In the first seven experiments shown in Table III morphine in small doses was also used. Large doses of morphine depress the respiratory centre[1] so much that there may be a great accumulation of carbon dioxide in the blood. The result is a respiratory quotient which is too low. This effect has been witnessed a number of times in the course of this work. Thus, on one occasion, a dose of 7 c.c. of 1 per cent morphine was responsible for a fall in quotient from .83 to .76.

In all of the experiments in series A chloretone was given in saturated aqueous solution (30 c.c. per kilo of body weight) by stomach tube. In series B it was given in solution in oil (1 gm. of substance to each 3 kilos of weight) by intraperitoneal injection. The latter mode of administration ensures more rapid absorption and hence produces a more profound state of narcosis. The oxygen absorption calculated to the basis of the unit of surface area (Table III) is, for this reason, much less in the later than in the earlier experiments. The mean blood pressures were uniformly higher where morphine was used.

Comparison of the Criteria of Metabolism in the Anaesthetized Dog. — Because the store of carbon dioxide in the body is subject to depletion through increased respiratory activity caused in the various ways mentioned above and because the store of oxygen is not subject to great change, the total amount

[1] Cushny: Text book of pharmacology, 1910, p. 221; also Filehne and Kionka: Archiv für die gesammte Physiologie, 1895–96, lxii, p. 201.

carried by the blood at any one time being not large, it seems best to limit the comparison of the criteria being studied to their relationship to the oxygen absorption. It is necessary, also, for reasons already given, to exclude from comparison the two periods given in Table III where the chest was opened.

From Table IV it may be seen that, in the anaesthetized dog, the pulse rate is, on the whole, a better guide to the oxygen absorption than is the total heart action. In Experiment 4, where the heart rate was very rapid, brought about by artificial respiration in the second period, the heart rate is not a good guide; but in Experiment 5, where not only the heart rate but the mean pressure was greatly altered by the artificial respiration, the heart rate is a better guide than the total heart action. The pulse pressure in the second period of this experiment is considerably augmented, due, apparently, to the greater distensibility of the arterial system at the lower mean pressure (see below). The product, therefore, of pulse pressure by pulse rate is out of all proportion to the slight increase in metabolism.

With the thought that hemorrhage would be a satisfactory means of testing this influence of mean pressure on the pulse pressure and so on the product (PP $\times$ PR) in its relation to metabolism, the last three experiments terminated with a period following, in each case, the withdrawal of a considerable volume of blood. The mean pressures fell (see Table III) to approximately two-thirds that prevailing in the control period just preceding. The pulse pressures in each case also fell; but fell a little too much, in proportion to the increase in heart rate, to keep up the product (total heart action.) The oxygen absorption is slightly lower in two of the three experiments and in the third is almost the same as in the control period. The tendency, therefore, plainly is, for the product (PP $\times$ PR) rather than the pulse rate, to run parallel to the absorption of oxygen after hemorrhage (last periods for experiments 13, 14, and 15, Table IV). It would appear, from this, that a fall in blood pressure after hemorrhage has a very different effect from a fall in pressure of approximately the same extent produced by overventilation when there was no change in the volume of the circulating fluid. The one condition brings about a rise in pulse pressure, the other a fall. The deter-

TABLE IV

COMPARISON OF CRITERIA FOR ABSORPTION OF OXYGEN

Exp. No.	Dog	Period	$\frac{PP \times PR}{O_2}$ c.c. per min.	Per cent variation	$\frac{PR}{O_2}$ c.c. per min.	Per cent variation
1	XXV	I	56		0.69	
		II	52	− 7.1	0.57	− 17.4
3	XXVII	I	20.4		0.53	
		II	22.8	+ 11.0	0.52	− 1.9
4	XXVIII	I	27.6		1.07	
	Artificial respiration	II	30.4	+ 9.2	1.52	+ 42.0
5	XXXII	I	43.2		1.98	
	Art. resp.	II	71.8	+ 66.2	2.11	+ 7.6
6	XXXIII	I	41.7		0.84	
		II	37.0	+ 11.2	0.86	+ 2.4
8	XXXVI	I	18.3		0.61	
		II	18.5	+ 1.1	0.61	± 0.
9	XXXVIII	I	70.7		2.14	
		II	61.2	—13.4	2.18	+ 1.8
10	XL	I	67.2		1.74	
		II	62.4	− 7.1	1.93	+ 10.9
12	XLII	I	124		2.40	
		II	140	+ 11.1	2.64	+ 9.0
13	XLIII	I	97.5		2.42	
	After hemorrhage	II	94.5	− 3.0	2.69	+ 11.1
		III	90.7	− 4.0	3.24	+ 20.9
14	XLIV	I	66		1.83	
	After hemorrhage	II	63	− 4.5	1.92	+ 4.9
		III	55	− 12.7	2.24	+ 16.7
15	XLV	I	41		1.70	
	After hemorrhage	II	37	− 9.7	1.57	− 7.6
		III	34	− 8.1	1.86	+ 11.8
	Average variation			11.9		11.1
	Excluding artificial respiration and hemorrage periods			7.92		6.7
	Excluding artificial respiration only			8.00		10.1

mining factor plainly would be the actual amount of blood discharged by the heart at each systole, a matter which will be considered presently.

Omitting from comparison all the hemorrhage periods and the periods in which artificial respiration was used, it is found that the heart rate is still a slightly better guide to the absorption of oxygen. When the hemorrhage periods are included, the periods of artificial respiration only being dropped, the total heart action becomes a better guide. The thought is suggested that, under all naturally occurring variations of activity in the circulatory system, including hemorrhage as a form of accident against which nature has had an opportunity to evolve a protective mechanism, the total lift above diastolic pressure to which the heart must raise the pressure in order to deliver a unit amount of oxygen to the tissues is uniform (to within $\pm$ 8 per cent).

The fact that the fraction of a heart beat or number of beats $\frac{(PR)}{O_2}$ necessary to perform this unit of circulatory work is nearly as uniform ($\pm$ 10.1 per cent) makes it appear, at first sight, that the pulse volume is on the average nearly uniform and that the real variable, as Henderson[1] has insisted, is the pulse rate. Were this true, the real minute volume, i.e., pulse volume (or systolic output) multiplied by the heart rate, should run perfectly parallel (barring considerable changes in the composition of the blood on the two sides of the heart) to the oxygen absorption.

Comparison of Minute Volume and Pulse Volume with Oxygen Absorption. — It would lead too far to attempt here a discussion of the methods of determining minute volume. From their brief experience, the writers confess to a feeling of distrust of any cardiometric method, and have resorted to the method proposed by Fick[2] and first employed by Gréhant and Quinquaud[3] on the dog and by Zuntz and Hageman[4] on the horse,

[1] Henderson, Y.: This journal, 1908–09, xxiii, p. 345; 1913, xxxi, p. 288.

[2] Fick: Sitzungsberichte der physikalische-medizinischen Gesellschaft zu Würzburg, 1870, p. 161.

[3] Gréhant and Quinquaud: Comptes rendus de la Société de biologie, 1886, p. 159.

[4] Zuntz: Deutsche medizinische Wochenschrift, 1892, p. 129.

as the most reliable method yet proposed. Briefly stated, the minute volume is found by dividing the volume of oxygen (much more reliable than the volume of carbon dioxide) absorbed into the blood from the lungs in one minute of time by the percentage (by volume) increase in the oxygen of the arterial blood over that of the venous blood. Obviously, the oxygen must be correctly determined and the blood analyses must be perfectly reliable. The work of Krogh [1] appears to have proven conclusively that the exchange of gases takes place only by diffusion.

Using the methods already described, the writers have estimated the minute volume in a number of the experiments already tabulated. For the present purpose, only experiments where there were two or more adjacent periods showing a difference in the oxygen absorption can be employed. Table V exhibits the results from five such experiments, including one where artificial respiration was resorted to and two in which a large amount of blood was drawn. In all of these experiments the two samples of blood were drawn, by means of Brodie's pipettes, either simultaneously or the arterial just before the venous sample, from the right heart through a sound introduced by way of the jugular vein and from the carotid artery. All analyses were done in duplicate.

Referring to the table and noting first the perfectly normal experiment, No. 8, it is seen that the minute volume runs very closely parallel to the oxygen absorption. In the column showing the ratio of minute volume to the oxygen absorption, or differently expressed, the number of cubic centimetres of blood taking up 1 c.c. of oxygen, there is, with a thirteen per cent increase in oxygen absorption, a variation of only 3.2 per cent. There is, however, in this case a perfect parallelism (Table IV) between the pulse rate and the oxygen absorption. Hence it follows, as a logical necessity, that the pulse volumes must be nearly equal in the two periods and this proves, in fact, to be the case. The syllogism would run thus: The pulse rate being proportional to the oxygen absorption, and the gain in oxygen by the blood (per cent increase from venous to arterial) being the same in the two periods, the pulse volumes necessarily are equal. This will be clearer if we take a concrete case with simple whole numbers. Suppose

[1] Krogh: Skandinavisches Archiv für Physiologie, 1910, xxiii, p. 248.

the oxygen absorption in two periods to be 200 and 250 c.c. per minute. The average pulse rate in the same two periods is 100 and 125, i.e., strictly proportional. Now, if the amount of blood moved through the lungs with each systole were the same in the two periods, it would follow that the gain in percentage of oxygen by the blood would be the same in the two periods; or, to turn the last two propositions around, if the gain in percentage by the blood in the two periods were the same, the average pulse volumes would necessarily be equal. Experiment 8 fulfils these conditions almost perfectly. Turning to Experiment 9 we find that, while the pulse rate is proportional to the oxygen absorption (Table IV), the minute volumes are not quite so, and, on reflecting in terms of the simple whole numbers just used, it becomes apparent that the pulse volumes cannot be equal. Thus, suppose again, 200 and 250 c.c. represent oxygen absorption, 100 and 125 the pulse rates in the two periods. If the gain in percentage of oxygen by the blood should be greater in the second period than in the first, it would follow that the pulse volume in the second would be less than in the first. Experiment 9 fulfils these conditions. It happens that the gain in percentage of oxygen by the blood in going through the lungs is nearly proportional to the increase in oxygen absorption, i.e., the minute volumes are almost equal in the two periods.

An easy transition from these conditions, so far as pulse volume is concerned, is represented by Experiment 5, only the order is reversed. We are going here from a smaller to a larger pulse volume. The pulse rate again is nearly proportional to the oxygen absorption (Table IV), but the minute volume is far from being proportional. The percentile gain in oxygen by the blood is twice as much in the first period as in the second. Hence, the pulse volume in the second must be twice as much as in the first. Putting it a little differently, the same amount of oxygen is forwarded to the tissues by a single systole in the two periods. But in the second period that amount of oxygen is contained in twice as much blood.

The hemorrhage experiments present a different set of premises. Instead of the pulse rate it is the product of pulse rate and pulse pressure which is proportional to the oxygen absorp-

TABLE V

THE MINUTE VOLUME AND PULSE VOLUME AS A MEASURE OF OXYGEN ABSORPTION

Exp. No.	Dog No.	Period	Arterial		Venous		% Dif. in O_2	O_2 abs. per min. c.c.	Min. vol. c.c.	No. c.c. blood taking up 1 c.c. O_2 [1]	Per cent variation	Pulse vol. c.c.	Pulse pressure	Mean pressure
			O_2 per cent	CO_2 per cent	O_2 per cent	CO_2 per cent								
5	XXXII	I	14.83		5.21		9.62	86.	894	10.4		5.3	22	84
	Artificial respiration	II	14.84	41.79	10.64	49.28	4.20	95.5	2274	23.8	+ 128.8	11.2	34	56
8	XXXVI	I	B19.45	48.52	12.95	50.69								
			E14.43	44.09	8.26	50.44	6.33	242	3750	15.5		25.1	27	90
		II	E15.37	37.53	9.13	45.43	6.24	274.	4386	16.0	+ 3.2	26.1	30	108
9	XXXVIII	I	E17.51	38.43	13.33	42.05	4.18	70.1	1677	23.9		11.2	33	96
		II	E20.17	54.09	15.45	57.95	4.72	79.6	1688	21.2	− 11.3	9.7	28	115
14	XLIV	II	B16.39	50.49	11.30	55.74								
			E16.97	48.26	12.82	52.84	4.62	86.0	1881	21.8		11.1	33	99
	After hemorrhage	III	E16.78	46.78	7.72	54.71	9.06	87.0	985	11.3	− 48.1	4.9	24	56
15	XLV	II	B19.63	37.29	11.01	44.21								
			E19.37	39.67	13.42	43.93	7.28	87.7	1204	13.7		8.6	24	61
	After hemorrhage	III	E20.17	40.03	10.14	45.40	10.14	86.6	845	9.7	− 29.2	5.2	18	48

[1] Found by dividing minute volume by c.c. of O_2 absorbed per minute.

tion (Table IV). As a matter of fact, we may consider the oxygen absorption as not having changed — the figures are so nearly the same in the two periods. The product (PP × PR) is maintained (or nearly so) by a reduction in pulse pressure corresponding to the increase in pulse rate. It is rather startling at first sight to find that the minute volumes stand so far off the line of proportionality. In one respect, Experiment 14 is almost the exact reverse of Experiment 5, namely, that whereas in the second period of that experiment 1 c.c. of oxygen was transported by twice as much blood as in the first, here 1 c.c. is taken up, after hemorrhage, by approximately one-half as much blood (11.3 c.c. instead of 21.8). As a matter of fact, the hemorrhage amounted to nearly half the dog's total volume of blood (305 grams, the dog weighing 14.9 kilos). One is prepared, therefore, to find the gain in oxygen percentage in arterial over venous blood nearly twice as much as in the first period. Had the pulse rate been proportional to oxygen absorption, it then would have followed, as before, that the pulse volume would be one-half as much in the second period as in the first. The pulse rate being increased more than the oxygen absorption, i.e., less oxygen being transported with each beat, the pulse volume is necessarily less than one-half its volume in the former period.

Describing the conditions for Experiment 5 one could say that, while the same amount of oxygen was being forwarded to the tissues with each heart beat in the two periods, in the second period that amount was contained in twice as much blood as in the first. The facts for Experiment 14 can be put this way: The same total amount of oxygen is being forwarded to the tissues each minute, but, in the second period, it is taken up by only one-half as much blood. The heart delivers a unit volume of oxygen in this case, not by putting out the same quantity of blood, but (the oxygen absorption being proportional to PR × PP) by lifting the pressure to the same amount. The diastolic pressure against which the heart must work being less, the tax upon its energy is correspondingly less.

Similar changes, proportional to the lesser hemorrhage, can be followed in Experiment 15.

Relation of Pulse Volume to Pulse Pressure. — Space does not

permit a full discussion of this topic at this time. From the few data presented in Table V it might be inferred that the pulse pressure, accurately determined, is an approximate quantitative measure of the pulse volume. In two experiments (9 and 15), one with the Hürthle manometer and the other with the optical, it is very nearly proportional to pulse volume in spite of the fact that, in one experiment, the mean pressure rose and in the other it fell. Applying v. Recklinghausen's formula and assuming that k is perfectly constant, one could deduce [1] from these experiments that the coefficient $\left(\frac{dI}{dp}\right) k$ is the same at 96 mm. of Hg as at 115, and very nearly the same, in another dog, at 90 as at 108 mm. of Hg. Evidently, however, this would not apply to Experiment 5 or Experiment 14. The latter would give a value for $\left(\frac{dI}{dp}\right) k$ at 99 mm. Hg mean pressure of approximately $\frac{1}{3}$, and at 56 mm. a coefficient of $\frac{1}{5}$, i.e., the distensibility would be greater, as we should expect, at the lower pressure. Experiment 5 would give reverse results — value for $\left(\frac{dI}{dp}\right) k$ of $\frac{1}{4}$ at 84 mm. and of $\frac{1}{3}$ at 51 mm. mean pressure. After hemorrhage the dilution of the circulating fluid by lymph would, of course, affect the viscosity and k would no longer be constant. A profitable line of inquiry would be to combine pulse pressure and pulse volume determinations with measurements of viscosity at different intervals after hemorrhage. The authors wish expressly to state that they do not regard the data here presented as sufficient to warrant conclusions regarding the pulse pressure as a measure of pulse volume or regarding the variations in distensibility at different mean pressures.

Summary

1. Experiments on the human subject, in which the respiratory metabolism and the heart action were determined simultaneously while the subject was resting and while doing a moderate amount

[1] From $A = \frac{R}{\left(\frac{dI}{dp}\right)} \times \frac{1}{k}$ it follows that $k \left(\frac{dI}{dp}\right) = \frac{R}{A}$

Cf. Mohr: *loc. cit.*

of muscular work, show that the product of pulse pressure (Erlanger) by the pulse rate is a slightly better index of the oxygen absorption than the heart rate alone. A low ratio $\left(\frac{PP \times PR}{O_2 \text{ cc. per min.}}\right)$ is found in subjects who are muscularly well trained, and a high ratio is found in subjects not in muscular training. The figure obtained by dividing this product in millimetres of mercury by the number of cubic centimetres of oxygen absorbed per minute, expresses the number of millimetres of mercury arterial pressure overcome by the left ventricle in order to deliver one cubic centimetre of oxygen to the tissues. This number was found to range from 6.7 in a well-trained individual to 13.6 in a fasting subject.

2. A single experiment on the influence of a bath at 10° C. is in agreement with results by the Plesch and Bornstein methods, showing that the pulse volume is increased. The product (PP × PR) is very closely parallel to the oxygen asborption.

3. Alterations of the metabolism under the influence of foods, on the other hand, run more nearly parallel to the heart rate.

4. In all the experiments on the human subject the total heart action (PP × PR) is more nearly parallel to the oxygen absorption than to the carbon dioxide elimination.

5. Experiments on anaesthetized animals, in which alterations in the intensity of the metabolism were caused by variations in the depth of the anaesthesia, reveal slightly closer parallelism with the heart rate than with the product PP × PR.

6. After extensive hemorrhage, however, the product PP × PR is a better criterion of the oxygen absorption than is the pulse rate. It is also a much better criterion than the minute volume as determined by the Fick method.

7. When the oxygen absorption is proportional to the pulse rate, the pulse volume will vary inversely as the gain in oxygen percentage by the blood in passing the lungs. In other words, when the same amount of oxygen is forwarded to the tissues with each heart beat, a high percentage gain necessarily denotes a small pulse volume and *vice versa*.

THE INFLUENCE OF PARATHYROID TETANY ON THE LIVER AND THE PANCREAS

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RESULTS recently obtained by various observers indicate a diminished activity of the liver during parathyroid tetany. Hirsch[1] found a decreased sugar tolerance in dogs when dextrose was given by the mouth. Underhill and Saiki[2] report that when dextrose was injected subcutaneously, a much larger amount of sugar appeared in the urine after parathyroidectomy than before. The investigations of Eppinger, Falta, and Rudinger[3] seem to show a weakened assimilation power for glucose injected subcutaneously, when three parathyroids were removed. Such a loss in sugar tolerance on the part of dogs in parathyroid tetany must be due to one or both of two factors, viz., a diminished activity of the liver for forming glycogen or a depression in oxidation. An experiment by Underhill and Saiki[2] appears to show that it is not due to a deficiency of the liver function. They found the amount of glycogen present in the liver, following two subcutaneous injections of dextrose, to be about the same in a parathyroidectomized dog as in a normal dog.

The experimental results on nitrogenous metabolism, although somewhat conflicting, point also to an impairment in the functions of the liver. Especially convincing are the results obtained relative to the excretion of urea. Ver Ecke[4] was the first to note the reduction in the quantity of urea excreted after complete thyroidectomy. This point was further investigated by Greenwald,[5] Cooke,[6] and Juschtschenko[7] in parathyroidectomized dogs. Their results all verify that of Ver Ecke in that the amount of urea in the urine diminished during tetany. Granted that the liver is the principal seat of the production of urea, these investigations must be interpreted as at least indicating a possibility of weakened activity on the part of this organ. Coronedi and Luzzatto[8] on

the contrary failed to obtain a decrease of urea and concluded that the parathyroid insufficiency has no effect on the liver activity.

In regard to the excretion of ammonia the results are even more contradictory than in the case of urea. This is particularly true in regard to the concentration of ammonia in the blood during tetany. An increase in relative and absolute ammonia has been reported by Coronedi and Luzzatto,[8] MacCallum and Voegtlin,[9] Berkeley and Beebe,[10] Cooke,[6] and Underhill and Saiki.[2] Greenwald[5] states that the proportion of ammonia nitrogen to total nitrogen is about the same after parathyroidectomy as before. Juschtschenko[7] reports that, following parathyroidectomy, there was first a decrease in the urinary ammonia, which was followed by an increase in the later stages of tetany.

The concentration of ammonia in the blood of parathyroidectomized animals as compared with that of normal blood is certainly an open question. MacCallum and Voegtlin[9] reported that the concentration of ammonia increased in the blood of dogs during parathyroid tetany. A similar increase was observed by Carlson and Jacobson[11] in cats and foxes, as well as a depression in the ammonia destroying power of the liver. Miss Jacobson[12] even found that the concentration of ammonia in the blood of dogs and cats in parathyroid tetany was as high as when sufficient ammonia was injected into the circulation to produce ammonia tetany, and concluded that the parathyroid tetany might be due directly to the excess of ammonia in the blood. More recently, however, Carlson and Jacobson,[13] using Nessler's method for the determination of ammonia instead of the titration method, discovered no gain in the ammonia content of the blood. The results obtained by Greenwald[5] verify these later results of Carlson and Jacobson.[13] The fact that Greenwald[5] fed his dogs a fixed diet makes his results all the more convincing on this point. The results of Medwedew[14] on the ammonia content of the blood of normal, starved, and parathyroidectomized dogs seem to show that there is more ammonia in the blood of parathyroid tetany dogs. This observer noted that the amount of ammonia set free from the blood for a period of twenty-four hours after the drawing was much higher for parathyroid tetany dogs than for normal animals

and lowest for starved dogs. He found that the blood drawn from an animal under aseptic conditions and allowed to stand at body temperature will show an increase or decrease of ammonia content during the course of twenty-four to thirty hours standing, depending on whether the "desamidase" or antiferment predominates. The ferment "desamidase" causes a setting free of ammonia and the antiferment a synthesis or binding of ammonia. The "desamidase" is higher during parathyroid tetany than during the normal condition. Following starvation the antiferment predominates. These results obtained by Medwedew show that it is important that the ammonia content of the blood be determined immediately after drawing. The conflicting results obtained relative to ammonia content of the blood of parathyroidectomized animals may be explained by Medwedew's observations.

Greenwald [5] obtained an increase in nitrogenous compounds of unknown nature in the urine of parathyroidectomized dogs. This author suggests that this indicates a depression of the liver. The increase in the amino acid nitrogen in the urine after parathyroidectomy would also indicate such a depression. Juschtschenko [7] found that the amino acids increased in the urine after parathyroidectomy. He used Sörenson's method for determining the amino acids and made observations on only two dogs. Cooke used Van Slyke's method for determining the amino acids and found no increase during parathyroid tetany.

The pathological changes of the liver in parathyroid tetany also point towards a depression of this organ. It must be remembered in this connection, however, that there can be a considerable degeneration of the liver without a marked depression in its physiological activity. Delitala [15] noticed various lesions of the liver following parathyroid tetany, but concluded that there was no constancy between the lesions observed and the thyro-parathyropriva syndrome. Morel and Rathery [16] made microscopic examinations of the livers of dogs before and after parathyroidectomy and found that hemorrhages occurred, but these were inconstant and not intense. The fatty changes were likewise not a constant feature and depended upon the diet. These investigators found, however, that the homogeneous condition of the

hepatic cells and islets was a constant characteristic. This feature was often coexistent with hemorrhages and an alteration in the number and form of the granules, fragmentation of the protoplasm, and the presence of large, greenish masses stuffing the cells. Koch [17] ascertained pathological changes in the liver cells as well as marked changes in the vessels of the liver.

The presence of lactic acid in the urine of parathyroidectomized dogs as observed by Cooke [6] led to the conclusion that there might be an impairment in the hepatic function of breaking up the lactic acid formed by the muscles.

Morel,[18] besides finding a decrease in the amount of urea and an increase in total and ammonia nitrogen, also reported the presence of diacetic and lactic acids in the urine of parathyroidectomized dogs. He showed that there is a decrease in the antitoxic functions of the liver during experimental suppression of the parathyroids.

In view of the fact that there is considerable evidence for liver depression, and taking into account that the results are contradictory, the work reported in this paper was undertaken in the hope of throwing more light on some of the phases bearing on liver activity in parathyroid tetany. Professor A. J. Carlson suggested the work and outlined the general plan of attack. The points investigated were sugar tolerance, concentration of fibrinogen in the blood, excretion of amino acids in the urine, and the secretion and some properties of the bile. The work on the secretion of pancreatic juice was an outcome of the results obtained on the excretion of amino acids in the urine.

I. The Effect of Parathyroid Tetany on the Physiological Activity of the Liver

1. Sugar Tolerance in Normal and Thyro-parathyroidectomized Dogs. — In previous work on sugar tolerance the experiments have been conducted by feeding sugar by mouth or by subcutaneous injections of dextrose. Feeding sugar to dogs in tetany by mouth is undesirable on account of the vomiting and the depression of the digestive tract. Subcutaneous injections of sugar are at best a severe treatment. The best method for investigat-

ing this question seems to be by intravenous injections of sugar. In these experiments we injected into the saphenous vein of the dog sufficient twenty per cent solution of dextrose in physiological salt solution to make one or one and one half grams per kilo of body weight. Professor Carlson had previously found that normal dogs tolerate about one gram of glucose per kilo of body weight injected intravenously. In several of the beginning experiments only one gram of dextrose per kilo of body weight was injected, but in some of these cases no sugar or only traces appeared in the urine. One and one-half grams per kilo of body weight were therefore used in the injections in the rest of the experiments in order to make sure that there would be enough sugar in the urine to make successful determinations. Fehling's method was employed and the end point was determined by means of acidified potassium ferrocyanide or acidified starch iodide solution. The dogs were kept in metabolism cages and the diet was maintained nearly constant throughout the experiments. Dogs 16 and 17 were fed a standard diet. One or more injections of dextrose were made two or three days before parathyroidectomy and the amount of sugar in the urine voided during the following twenty-four hours was determined. Sugar was again injected while the dogs were in tetany. In some cases, when the tetany symptoms were mild, as many as five observations were made. In all cases the injections were at least twenty-four hours apart. The results of this series are given in Table I.

In order to be certain that the anorexia so frequent in dogs during parathyroid tetany was not a factor in the results obtained, sugar tolerance tests were made on four dogs before and after starvation periods of four to eight days. The following results were obtained:

Dog 8, sugar tolerance, normal 0.90 gm., after starvation 1.12 gm.									
Dog 9	"	"	"	1.42	"	"	"	1.40	"
Dog 10	"	"	"	1.42	"	"	"	1.34	"
Dog 11	"	"	"	1.43	"	"	"	1.34	"

The sugar tolerance is practically the same during starvation as during normal feeding except in dog 8, where it is somewhat increased after starvation.

TABLE I

THE EFFECT OF PARATHYROID TETANY ON THE SUGAR TOLERANCE

Nos. 1 to 6 received one gram of dextrose per kilo of body weight; the others one and one-half grams per kilo of body weight, intravenously. The figures represent averages of the number of tests indicated by the figures inclosed in parentheses.

Normal dogs				Parathyroidectomized dogs			
No.	Dextrose injected gm.	Dextrose in urine, total gm.	Sugar tolerance, gm. per kilo of body wgt.	Dextrose injected gm.	Dextrose in urine, total gm.	Sugar tolerance, gm. per kilo of body wgt.	Remarks
1	9.4 (1)	0.652	0.93	9.4 (1)	1.25	0.867	
2	10.4 (1)	0.761	0.927	9.18 (2)	0.199	0.919	Died 5 hr. after last injection.
3	7.6 (1)	1.117	0.853	6.76 (5)	1.32	0.801	
4	7.48 (1)	0.000	1.000	6.23 (2)	0.00	1.000	
5	6.85 (1)	0.712	0.896	6.24 (1)	trace	1.000	
6	7.68 (1)	0.614	0.92	7.13 (2)	0.61	0.91	
7	7.35 (1)	0.25	1.114	7.7 (1)	1.08	1.28	
9	14.76 (1)	0.765	1.421	11.85 (1)	2.23	1.217	Died 9 hr. after injection.
11	12.09 (1)	0.54	1.433	9.75 (1)	0.54	1.416	Died 2 hr. after injection.
12	8.16 (1)	1.09	1.299	8.01 (2)	0.97	1.316	Died 9 hr. after last injection.
13	10.23 (1)	1.09	1.341	9.84 (1)	1.61	1.254	
14	10.74 (1)	2.01	1.219	10.16 (5)	1.62	1.255	
15	11.28 (1)	1.01	1.365	11.19 (2)	1.72	1.269	
16	14 (2)	3.71	1.108	14 (1)	2.18	1.273	
17	15 (3)	2.88	1.212	15 (3)	3.18	1.181	

A study of Table I shows that in seven dogs there was a slight increase in sugar tolerance during parathyroid tetany, while in six dogs there was a slight decrease. These results show conclusively that parathyroid tetany has no effect on the tolerance of sugar injected intravenously. It might be expected that during the increased activity of the muscles in parathyroid tetany there

would be an increased oxidation of sugar. The results obtained by other observers following subcutaneous injections, however, seem to show that there is a decrease in the oxidation of sugar. The sugar injected intravenously is rapidly taken up from the blood, because the urine passed within a few hours following an injection contains all the sugar which is excreted. It is, therefore, reasonable to suppose that most of this sugar is taken up by the liver to form glycogen. If there is a decrease in the oxidation of sugar and the tolerance is not changed, there must be an increase in the glycogenic function of the liver proportional to the decrease in oxidation. These results, then, on sugar tolerance furnish evidence that there is no deficiency in the glycogenic function of the liver during parathyroid tetany. The results recorded above show that the loss of appetite is not a factor in the results obtained.

2. The Formation of Fibrin in the Blood of Normal and Parathyroid Tetany Dogs. — The researches of Nolf,[19] and Doyon, Morel, and Kareff[20] furnish conclusive evidence that the liver is the seat of the formation of fibrinogen. It was more recently found by Meek[21] that there is no regeneration of fibrinogen in the blood of dogs following the extirpation of the liver by Eck's fistula, and ligation of the portal vein and hepatic artery. Since the liver is the principal seat of the formation of fibrinogen, the fibrin formation in the blood drawn from a parathyroidectomized dog as compared with that drawn from the same dogs in the normal condition ought to throw some light on this function of the liver. Such experiments were conducted on six dogs. Fibrinogen determinations as fibrin were made on blood drawn from the saphenous vein before parathyroidectomy and during parathyroid tetany. The blood was collected in a dry, weighed beaker, defibrinated by beating, weighed, water containing some of the washings from a previous coagulation added, and the blood again beaten. The fibrin was collected on a filter of known weight, washed with normal salt solution until free from color, extracted with boiling alcohol, then with ether, dried at 115° C., cooled and weighed. The specific gravity determinations were made by Hammerschlag's method. The blood obtained after parathyroidectomy was always drawn while the animals were in tetany. The results obtained in these experiments were as follows:

		Fibrin percentage	*Sp. gr. of blood*
Dog 24	Normal	(2) 0.66	..
	Tetany	(1) 0.84	..
Dog 25	Normal	(3) 0.34	..
	Tetany	(2) 0.50	..
Dog 26	Normal	(3) 0.34	..
	Tetany	(7) 0.56	1.043
Dog 27	Normal	(3) 0.33	1.051
	Tetany	(4) 0.41	1.049
Dog 28	Normal	(2) 0.52	1.046
	Tetany	(1) 0.45	1.045
Dog 29	Normal	(2) 0.51	1.052
	Tetany	(2) 0.76	1.053

In the data just recorded the figures are averages of a number of determinations indicated by the figures in parentheses. The above figures show an increase in the percentage of fibrin in the blood during parathyroid tetany in all except one of the experiments, dog 28. The specific gravity of the blood remained unchanged during tetany. The results obtained, therefore, verify those of Albertoni [22] in regard to the formation of fibrin. This observer, however, found an increase in the specific gravity of the blood during tetany and attributed the increase in fibrin to that cause. My results on fibrin formation furnish conclusive evidence that there is no depression in the fibrinogen forming activity of the liver. They indicate, if anything, an increase in the formation of fibrinogen by the liver or a decrease in the rate of the destruction of fibrinogen in the blood.

3. The Excretion of Amino Acids during Parathyroid Tetany as compared with Normal and Starved dogs. — Glaessner [23] reported a marked rise in the output of amino acids in the urine during various pathological conditions of the liver. An increased discharge of amino acids in the urine would, therefore, indicate a deficiency in the function of the liver. In this part of the work the total amount of amino acids and ammonia excreted per day

in the urine was determined for definite periods before and after parathyroidectomy. The amount of amino acids was determined by the formal titration method as described by Frey and Gigon.[24] In this method ammonia is removed from the urine before the titration for amino acids. Two series of experiments were carried out. In the first series, the results of which are reported in Table IV, the dogs were fed the same amount of food, consisting of meat and bread, each day.

TABLE II

THE EXCRETION OF AMINO ACIDS IN THE URINE OF DOGS BEFORE AND AFTER PARATHYROIDECTOMY. THE FIGURES ARE AVERAGES PER DAY FOR NUMBER OF DAYS STATED.

		Normal				After parathyroidectomy				
No.	Wgt. kilos	No. of days	Average urine per day c.c.	NH_2 N total mg.	NH_3 N total mg.	No. of days	Average urine per day c.c.	NH_2 N total mg.	NH_3 N total mg.	Remarks
35	5.18	13	79	59.6	....	18	45	24.5	....	Cachectic, no severe tetany.
36	7.14	6	112	64.5	....	10	53	15.39	....	Cachectic, no severe tetany.
37	7.42	4	134	66.	222.2	3	134	45.	226.4	Tetany third day.
38	7.26	6	124	72.6	214.5	6	132	61.6	219.4	Tetany every day.
39	8.08	3	149	80.6	272.7	8	76	42.9	196.1	Tetany every day.

The dogs would usually eat their normal diet until the second or third attack of tetany set in. It was found that it was useless to attempt to feed dogs by stomach tube on account of the vomiting, which always follows. In this series of experiments the total amount of amino acids excreted per day during the period following parathyroid tetany is less than that excreted during the normal period. The decrease in the amino acids in the series can probably be accounted for by the loss of appetite.

A second series of experiments was conducted, in which a standard diet was fed to the dogs. This diet consisted of beef

TABLE III

THE AMINO ACID CONTENT OF THE URINE OF DOGS, COMPARING NORMAL DOGS ON A STANDARD DIET AND PARATHYROID TETANY DOGS ON A SIMILAR DIET, STARVATION PERIODS OF NORMAL AND PARATHYROIDECTOMY DOGS, AND NORMAL AND PARATHYROID TETANY DOGS ON STANDARD MIXED DIET AND NON-PROTEIN DIET

		Normal				Starved				After parathyroidectomy			
No.	Wgt. kilos	Days	Urine c.c.	NH_2 N total mg.	NH_3 N total mg.	Days	Urine c.c.	NH_2 N total mg.	NH_3 N total mg.	Days	Urine c.c.	NH_2 N total mg.	NH_3 N total mg.
40	6.6	5	385	83.	162.	5	131	41.3	137.	7	305	50.7	154.
41	7.36	5	334	51.98	132.	7	57	38.08	85.	—	—	—	—
42	7.14	5	512	91.5	268.	5	99	67.2	226.	—	—	—	—
43	7.18	10	187	52.34	142.4	5	56	35.49	74.5	5	49	30.56	73.2
44	10.74	10	316	95.3	247.	5	78	59.4	139.2	5	149	63.6	106.9
						Non-protein diet				Non-protein diet			
45	8.4	10	250	57.28	173.8	5	253	43.31	151.4	3	228	32.14	122.
46	10.8	10	441	87.	366.	5	401	51.	299.8	5	131	54.6	257.
47	6.7	10	292	57.53	169.	5	313	39.41	196.	5	215	31.61	83.

No. 40, fed during the tetany period. Nos. 41 and 42, no data during tetany. Nos. 43 and 44, starved during tetany period.
No. 45, in tetany the third day. No. 46, anorexia after the second day.

heart, lard, sugar, and starch, sufficient for the calorific requirements and to maintain the nitrogenous equilibrium. A little bone ash was added to prevent diarrhoea. These results are reported in Table III. Dog No. 40 lived seven days after the thyro-parathyroidectomy, showed tetany the second day, and ate the complete diet every day. There was no increase in amino acids or ammonia during this period. No data could be obtained on dogs Nos. 41 and 42 as they died in the first attack of tetany, which came in less than twenty-four hours following the operation. In dogs Nos. 43 and 44 a feeding period of five days was run, followed by a starvation period of five days, then another feeding period of five days followed by a starvation period, at the beginning of which the parathyroidectomy was performed. In No. 43 the amino acid content of the urine is a little lower during the tetany starvation period than during the normal starvation period, while in No. 44 it is a little higher during the tetany period. In Nos. 45, 46, and 47 the dogs were fed a mixed standard diet for five days, a non-protein diet for five days, then a mixed diet again for five days, followed by parathyroidectomy. They were fed the non-protein diet after the removal of the parathyroids. There is again no marked rise or fall in amino acids in the urine during the parathyroid tetany period as compared with the non-protein diet period. The results above recorded show that the total amino acids excreted in a day in parathyroidectomized dogs is no higher than that in normal dogs. These results, therefore, substantiate those obtained by Cooke[6] on this point. Again there is no evidence for depression of the liver in parathyroid tetany.

It was not the purpose in these experiments to investigate the ammonia excreted in the urine of parathyroid tetany dogs in this series, but since the ammonia had to be removed from the urine by Folin's method before the amino acids were determined, it was collected in standard acid and determined either by titration or Nesslerization or both. An examination of the tables will reveal the fact that there was no appreciable increase in the ammonia in the urine during parathyroid tetany. There was, in fact, a decrease in most cases. This furnishes additional evidence against liver depression during parathyroid tetany.

4. The Effect of Parathyroid Tetany on the Secretion of Bile and the Formation of Bile Acids by the Liver Cells. — Biliary fistulas were made by the method described by Pawlow. The flap of the intestine containing the papilla of the bile duct was transplanted into the abdominal wall. As soon as the wound was properly healed the bile was collected by means of a funnel made

TABLE IV

THE EFFECT OF PARATHYROID TETANY ON THE SECRETION OF BILE AND THE FORMATION OF BILE ACIDS BY THE LIVER. THE FIGURES ARE AVERAGES FOR NUMBER OF DAYS INDICATED BY FIGURES IN PARENTHESES.

Normal				Tetany		
No.	Hr. of bile collection	Bile c.c.	Bile acids total per hr. gm.	Hr. of bile collection	Bile c.c.	Bile acids total per hr. gm.
48	6.5	21 (4)	0.07	6.5	22 (5)	0.009
49 [1]	7	40 (3)	0.29	7	21 (6)	0.15
50	2	13 (5)	0.19	2	4.7 (4)	0.14
51	2	9 (2)	0.18	2	3.3 (6)	0.035
52	2	11 (3)	0.15	2	6 (4)	0.11
53	3	16 (4)	0.11	3	3 (1)	0.014
54	3	9 (4)	0.038	3	1.5 (8)	0.009
55	5	10 (8)	0.031	5	2 (1)	0.010

[1] Dog did not develop tetany.

to fit the abdomen. The bile was collected in each dog for a definite period (two to seven hours) after feeding. The diet was kept nearly constant and was always mixed with about 10 c.c. of bile from the previous day. In all but the last experiment the diet consisted of bread and milk nearly free from cream. In the last experiment the dog was fed on a meat diet exclusively. In a few cases the dogs in parathyroid tetany could not be induced to eat. The bile acids were determined by the colorimetric method using Pettenkofer's test. It was observed that the coloration in

this test varies directly with the concentration of bile acids present. The bile was decolorized by animal charcoal, and the bile acids extracted, after drying over a water bath, with hot alcohol.

Pettenkofer's test was applied to this mixture and the tube compared with tubes of a known amount of bile salts. This method may not be accurate for quantitative determination of bile acids, but seems sufficiently accurate for comparative study such as was made in this case. There seems to be no better method for determining bile acids except to make complete analysis of the bile, which, of course, could not be done in these experiments. The results of this series of experiments are given in Table IV. There is a decrease in the secretion of bile after the removal of the parathyroids in all but one experiment. There is also marked fall in the total bile acids. The percentage of bile acids was about the same before and after parathyroidectomy except in the dog which showed no decrease in secretion of bile. In this case the concentration of bile acids diminished very markedly. There seems to be no doubt, therefore, that the secretion of bile and the formation of bile acids by the liver cells are distinctly diminished during parathyroid tetany. Whether the apparent depression in this function of the liver is due specifically to the absence of the parathyroid secretion or indirectly to the condition of the digestive tract is another question. The fact that there was no depression in the other functions of the liver would be a point against a specific relation of the parathyroid secretion to the activity of the liver.

II. The Effect of Parathyroid Tetany on the Secretion and the Composition of the Pancreatic Juice

The evident decrease in amino acids in the urine of parathyroid tetany dogs in the above mentioned experiments suggested that there might be a depression in the action of the digestive juices. The anorexia, vomiting, and gastero-enteritis so frequent during parathyroid tetany in dogs also suggested that, in addition to the increased irritability of the stomach, there might be a depression in the digestive activity. In fact, Carlson found that food remains a longer time than normal in the stomach and

the intestines during parathyroid tetany. The results he obtained gave very strong evidence of a depression of the gastric and intestinal digestion.

Pancreatic fistulas were made according to Pawlow's method. A piece of the intestine containing the papilla of the ductus Santorini was transplanted into the abdominal wall and, as soon as the wound was healed (six to twelve days), the juice was collected by means of a wick extending from the papilla into a funnel fitted on the abdomen. The enterokinase secreted by the piece of intestine surrounding the papilla may be sufficient to activate the trypsin, but some enterokinase was prepared and added to make certain that the trypsinogen was all changed to trypsin. The dogs were fed an equal quantity of milk each day and the juice was collected for three hours after feeding. In a few cases juice was collected for an hour before feeding to determine the rate of flow without feeding. It was found that when the periods for collecting were made longer the abdomen became so corroded by the action of the juice that the juice would become stained with blood. This work, therefore, bears only on the juice collected for three hours following feeding and in a few cases that immediately before feeding, i.e., twenty-three hours after feeding. The results of this series are given in Table V. It will be seen that there is a very noticeable fall in the secretion of the pancreatic juice during parathyroid tetany. That this is not entirely due to the failure of the animal to eat, is evident from the fact that the juice flowed more rapidly in the normal dogs before feeding than in the dogs in parathyroid tetany. Besides, the dogs would usually take some milk during the first attacks of tetany, which, on account of the milk diet, were somewhat mild. In Nos. 56 and 57 the amount of trypsin was determined by the method of Gross.[25] In Nos. 58, 59 and 60 the tryptic action was determined by the Mett's tube method as described by Cobb.[26] There was no marked change in the proteolytic action of the juice except in Experiments 57 and 60. The diastatic action was determined by Wohlgemuth's method.[27] There was no constant variation in the diastatic action. The alkalinity of the juice was not effected. The same was true of the solids.

In Experiment 60 the secretion during the first day of tetany

was as high as normal but there was no action on the Mett's tube and the diastatic action was diminished. On the second day the secretion of juice had fallen to almost nothing, although the papilla seemed to be in good condition.

The results obtained, although not very extensive, furnish strong evidence that there is a marked depression in the secretion

TABLE V

THE EFFECT OF PARATHYROID TETANY ON THE SECRETION AND THE PROPERTIES OF THE PANCREATIC JUICE

The figures represent the averages for the number of days indicated by the figures in parentheses

No.	Juice collected for 3 hr. after feeding c.c.	Alkalinity	Solids	Tryptic action	Diastatic action	Remarks
56	26.5 (2)	0.38	....	5	8	Normal
	9 (1)	0.36	....	6.6	8	Tetany
57	18 (3)	0.40	3.21	10	12.5	Normal
	8 (3)	0.40	3.35	4.3	12.5	Tetany
58	17.5 (2)	0.26	3.94	2.1	7.5	Normal
	14 (5)	0.38	3.70	1.9	6.06	Tetany
59	25 (2)	0.28	3.65	2.4	7.8	Normal
	12.5 (2)	0.40	3.48	2.3	6.7	Tetany
60	18 (3)	0.23	3.40	2.7	4.3	Normal
	12 (3)	0.23	2.30	1.0	3.6	Tetany

of the pancreatic juice and depression of digestion. It was frequently observed that the stomach was filled with undigested food after death from parathyroid tetany. This was true even when the animals had refused food for two or three days before death. It was also noticed that the tetany symptoms were more violent when the dogs were fed exclusively on a meat diet than when they were starved or fed on a non-protein diet after the parathyroidec-

tomy. It is possible that the hyperexcitability during parathyroid tetany can be partly accounted for by the irritation of the nerve endings in the digestive tract caused by the undigested food. The similarity of gastric and infantile tetany to parathyroid tetany also favors such a conclusion. However, this point needs further investigation.

Summary and Conclusions

1. During parathyroid tetany there is no change in sugar tolerance in dogs, when the sugar is injected intravenously.

2. The percentage of fibrin in the blood drawn from parathyroid tetany dogs is greater than that drawn from normal dogs.

3. The excretion of amino acids and ammonia in the urine of parathyroidectomized dogs is not different from that observed in the animals in a normal condition.

4. There is a distinct decrease in the secretion of bile during parathyroid tetany. The concentration of bile acids remains the same but the total bile acids formed by the liver cells is diminished in direct proportion to the secretion of bile.

5. During parathyroid tetany the secretion of pancreatic juice is less than that in the normal dog before and after feeding.

6. There appears to be no deficiency in the functions of the liver in parathyroid tetany except in the secretion of bile. This depression is probably not due specifically to the absence of the parathyroid secretion but to the condition of the digestive tract.

7. The marked decrease in the secretion of pancreatic juice during parathyroid tetany gives further evidence that the condition of the digestive tract is an important factor in the parathyroid tetany complex.

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THE EFFECT OF CHEMICAL PRODUCTS OF MUSCULAR ACTIVITY ON THE FREQUENCY AND FORCE OF THE HEART BEAT

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Introduction

INTEREST in the possible role of products of muscular activity in the cardiac acceleration due to muscular exercise began with the experiments of Mosso,[1] in which an increase of heart rate was produced in the resting animal (dog) by the injection of blood from an animal fatigued by muscular exercise. Investigators since this time have attacked this problem by a number of different methods, and their studies have led to the advancement of several different explanations of the increase in heart rate as a result of activity of the skeletal muscles. So far as we have been able to find, such studies have been confined to experiments in the intact animal with the heart *in situ*, a condition which, in the light of recent work, makes it difficult to determine whether the effects observed are to be interpreted as a direct action on the heart, or result from indirect action on this organ through the intervention of some other mechanism of the body. Thus v. Anrep[2] has recently shown that the pressor action of products formed during asphyxia is in part due to stimulation of the adrenal glands. Experiments in which the action of fatigue products has been tested

on the heart *in situ* have been made by Johansson[3] and by Athanasiu and Carvallo.[4] These investigators observed the effect on heart rate of tetanization of the distal end of the sectioned spinal cord. In both series of experiments a slight acceleration of the heart occurred under these circumstances which persisted after section of the extrinsic cardiac nerves. The conclusion was, therefore, that there is some direct action of the products of metabolism on the heart independent of its extrinsic nerves, and that this action plays a role in cardiac acceleration in muscular exercise. This conclusion has been denied by Mansfeld,[5] who found that the effect described by Johansson and by Athanasiu and Carvallo is absent when means are used to prevent the blood which passes through the heart during the period of tetanization having a higher temperature than normally. He obtained negative results also from extracts of active muscles and from blood of fatigued animals when the influences due to change of temperature were controlled.

The demonstration by Geppert and Zuntz,[6] that the respiratory rate may be increased by metabolic products, has been a further stimulus to the study of the possible role that these play in cardiac acceleration. Certain substances known to be increased during muscular activity have been separately tested on the isolated mammalian heart perfused with saline solution, but the results from these researches would seem to furnish little evidence in reference to the effect of metabolic substances present in combination in the tissues or blood of the intact animal. The specific action of single products of metabolism has been found in certain cases to be antagonistic.[1]

In view of the contradictory results stated above, and in the absence of experimental results concerning the possible direct action of the combined metabolic products formed by the active muscles on the heart when indirect factors are excluded, we were led to

[1] Carbon dioxide was found by Jerusalem and Starling[7] and Ketcham, King and Hooker[8] to cause a slowing of the isolated mammalian heart. Bachmann[9] investigated the action of various nitrogenous extractions in Göthlin's solution on the isolated rabbit's heart. Sodium lactate in small quantities depresses; in larger amounts, equal to that which occurs in the blood after excessive muscular activity, acceleration was produced. Creatin in certain strengths increased the size of beat, but was without influence on the rate.

undertake the experimental work reported in this paper. We have employed the isolated and artificially perfused heart in all experiments, since it is only under these conditions that possible influences due to temperature changes, variations in blood pressure, or to indirect effects through other organs are excluded.

Method and Description of Experiments

In this series of experiments, six cats' hearts were perfused by Langendorff's method, using Locke's solution containing defibrinated cats' blood. The apparatus used for perfusion was that recently described by Eyster and Loevenhart,[10] in which the temperature of perfusion is controlled within narrow limits and in which a rapid change from one perfusion solution to another may be made. The hearts were rapidly removed and suspended in the apparatus immediately after free bleeding from the carotid under light ether anesthesia. Record of the rate and size of beat of the ventricles was obtained by direct connection of the apex of the left ventricle with a recording lever. Muscle extracts were made from resting or tetanized cats' muscles as follows: 200 gm. of thigh muscle was passed through a grinding machine and received in 200 cc. of 0.9 % NaCl at 37° C. This was placed in a shaking machine for four hours, the temperature being kept approximately constant, and then filtered through cotton wool. From 25 to 100 cc. of extracts made in this way were added to 4 litres of Locke's solution containing defibrinated blood from a cat which had not been subjected to stimulation. The first experiment served as a control to determine any possible influence of the extract of resting muscle. Experiments in which the effect of extracts from tetanized muscle was studied (III and IV) were further controlled by similar extracts from resting muscle previously perfused through the same heart. Since it was desirable to employ in these experiments hearts from animals which had been anesthetized lightly and for a short period of time, and also to have fresh extracts or blood for perfusion, two or more animals were used for each experiment. Fatigued muscle for extraction was obtained by anesthetizing an animal with ether, cutting the spinal cord in the lumbar region, and stimulating the distal end with a faradic current for periods of from three quarters

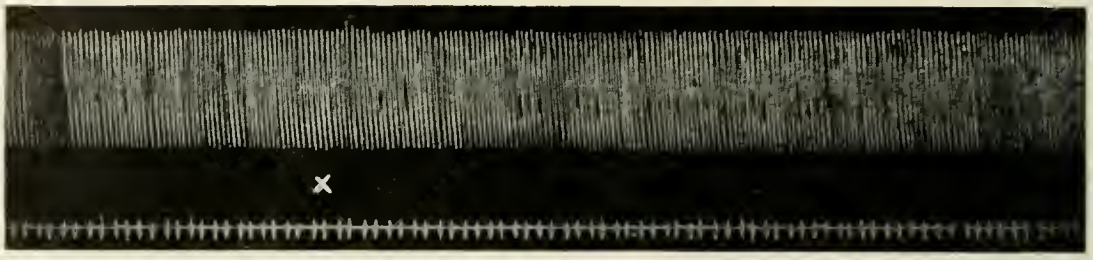

FIGURE 1. Experiment I. Shows the absence of effect on rate or size of beat from changing from normal perfusion to a perfusion solution containing extract of resting muscle (1 cc. of extract to 40 cc. Locke's solution containing defibrinated blood). In this and succeeding figures the lower line marks the time in intervals of one second. The upper line is a suspension curve of the ventricles, the upstroke of which represents systole. All records read from left to right. The mark X indicates the change from normal perfusion to perfusion with the extract.

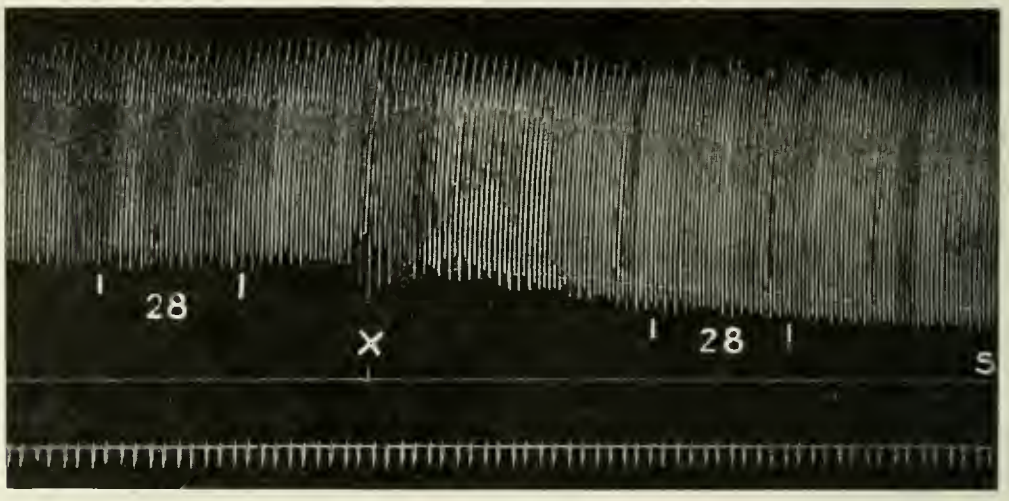

FIGURE 4A. Experiment IV. Increase of size of beat as a result of perfusion with blood from tetanized animal. The change to fatigue blood was made at X. The increase in size of contraction is mainly due to increased relaxation in diastole.

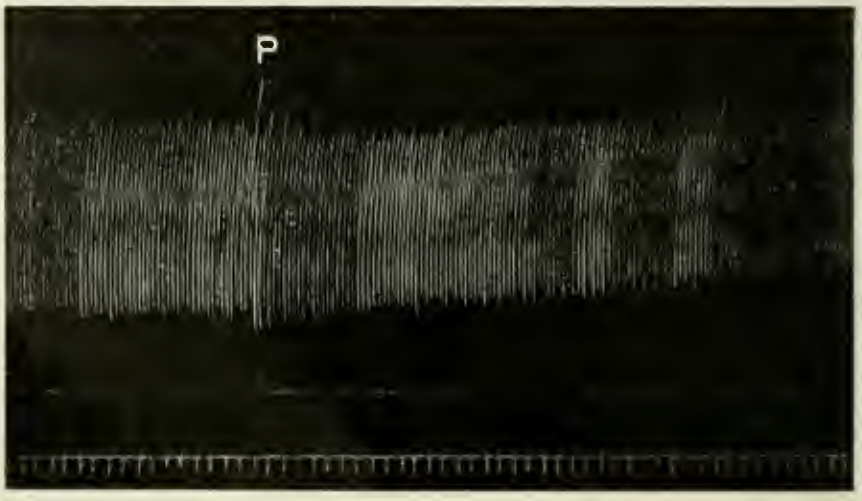

FIGURE 4B. Shows return to normal after the period of perfusion shown in 4a. The size of the beat is reduced and diastolic tone is rapidly regained.

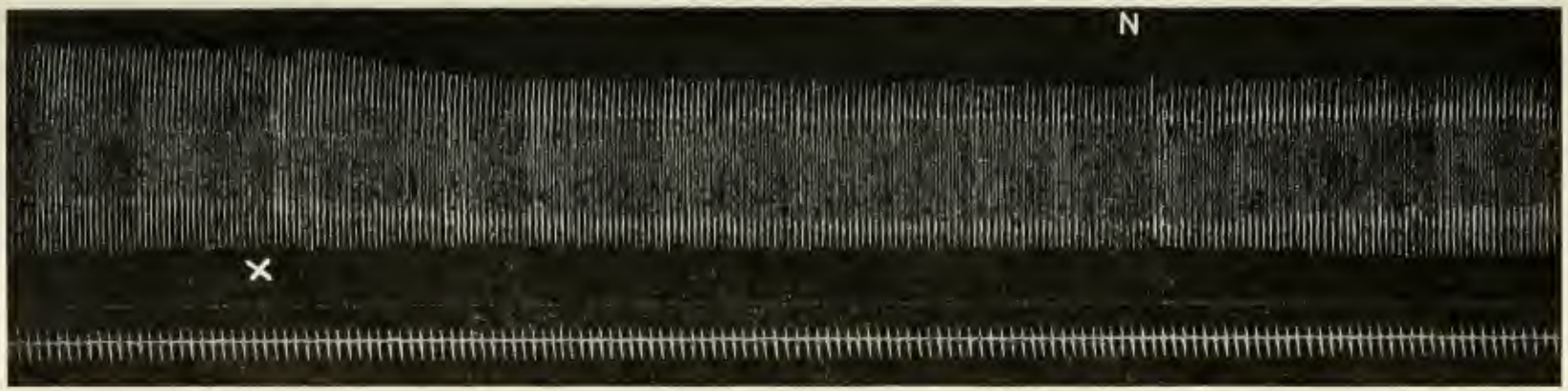

FIGURE 2. Experiment II. Shows the diminished beat as a result of perfusion with a strong extract (1 cc. to 40 cc. of Locke's-blood solution) of fatigued muscle. At the mark X change was made from the normal perfusion to perfusion with the extract. At N return was made to normal perfusion. The effect is mainly on the height of systole.

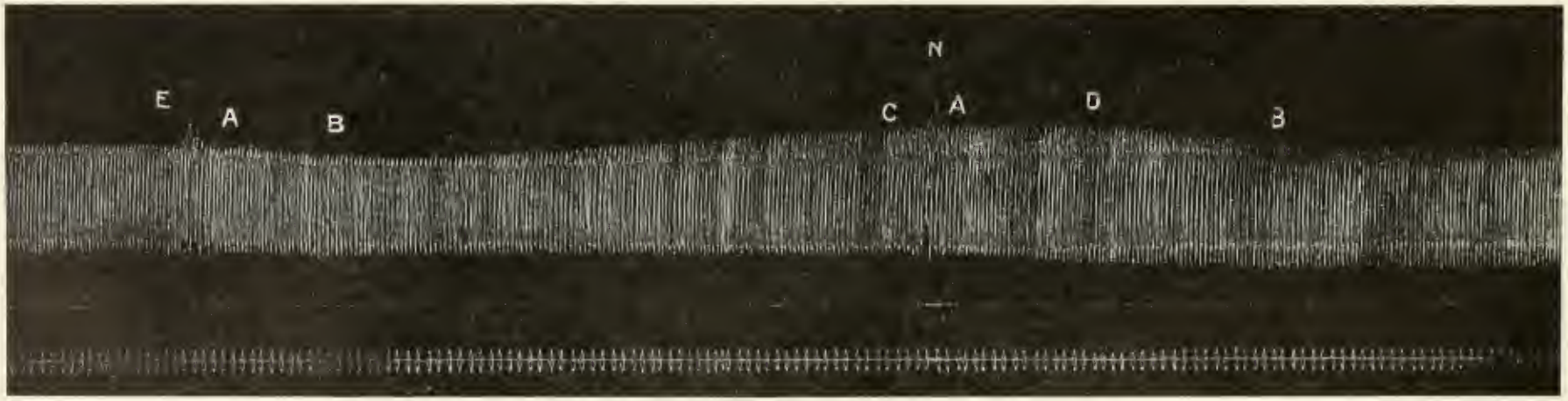

FIGURE 3. Experiment IV. Shows increase of size of beat as a result of perfusion with weaker extract (1 cc. to 160 cc. of Locke's-blood solution) of fatigued muscle. Change from normal perfusion to perfusion with extract was made at E, return to normal at N. The increase affects mainly systole, and in this case is preceded by transitory and slight decrease in size of beat.

to one and a half hours. Stimulation was stopped only when fatigue was sufficient to render the muscle no longer irritable to such stimulation. The thigh muscles were then quickly removed and extracted by the method described above. In one experiment (II) the whole limb was ligated except the nerve, in the others the normal blood flow was maintained in the limb throughout the period of tetanization. In two experiments (V and VI) the blood of the tetanized animal was employed instead of the extract from the muscle. Further points in reference to the details of the experiments will be found in the protocols.

Results

An extract from the resting cat muscle, made in the manner described above and used in a strength of 1 cc. of the extract to 40 cc. of the perfusion solution, was without effect on the isolated cat's heart. A corresponding strength of extract from muscle that had been tetanized under the conditions described above produced a slight decrease in size of beat, manifested as a diminution in extent of contraction, with no definite change in rate. Extracts from tetanized muscle of one-half and one-fourth this strength (Exps. III and IV) caused an increase in the size of beat. In the stronger solution this increase was transitory and was followed by a decrease. The increase usually affected both systole and diastole, resulting in an augmented height of contraction and an augmented relaxation in diastole (diminished diastolic tone). In other cases only the extent of systole was affected. The rate in each case was slightly reduced during perfusion with a solution containing the extract from tetanized muscle. Blood from a tetanized animal, when added to the perfusion fluid, produced a change similar to that caused by the weaker mixtures of extract; namely, a moderate increase in size of beat with no change or a slight decrease in rate. The increase was mainly and, in some cases, entirely the result of increased diastolic relaxation. Increased perfusion through the coronary arteries was present in Experiment IV during the period of increased contraction of the heart. Figures 1 to 4 give examples to illustrate the above statements.

Conclusion

Metabolic products, formed in active muscles, play no part in the increase in heart rate resulting from muscular activity, in so far as this action is upon the heart muscle directly or upon the cardiac endings of the extrinsic nerves. It seems probable, however, that such action may play a part in the increase in size of the heart beat observed under these circumstances.

Protocols

Experiment I. Control experiment to determine effects, if any, of extract from resting cat's muscle on isolated cat's heart. Cat anesthetized lightly with ether and killed by bleeding from carotid. 200 gm. of thigh muscle ground and extracted with 200 cc. NaCl at 37° C. in shaking machine for four hours. A second cat was then etherized and bled from carotid, blood defibrinated and added to the perfusion solutions. The heart from this cat was suspended in the apparatus and perfusion begun. The perfusion solutions employed were made up as follows:

Solution I. 4100 cc. Locke's solution, 65 cc. resting cat's blood.

Solution II. 4000 cc. Locke's solution, 65 cc. resting cat's blood, 100 cc. extract of resting muscle.

The temperature of perfusion throughout the experiment was 35.5, C.° the pressure 48 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.	Outflow in ccm. in 30 sec.
Normal (I)	60	15.0	11.5
	60	15.0	11.5
Extract (II)	59	15.0	11.0
	59	14.0	11.0
Normal (I)	57	14.0	11.0
	57	14.0	10.0
Extract (II)	58	13.5	10.5
	58	13.0	10.0

Experiment II. Effect of extract from tetanized cat's muscle with circulation cut off on isolated cat's heart.

First cat anesthetized, spinal cord exposed and cut. One posterior limb ligated with exception of sciatic nerve, and distal end stimulated for one hour with faradic current, the animal being kept alive and anesthetized during this period. Extract made from muscles of this leg by the usual procedure. Second cat was now anesthetized, bled from carotids, blood defibrinated, and heart suspended. The perfusion solutions used were made up as follows:

Solution I. 4100 cc. Locke's solution, 35 cc. resting cat's blood.

Solution II. 4000 cc. Locke's solution, 35 cc. resting cat's blood, 100 cc. extract of tetanized muscle.

Temperature of perfusion 35.5° C. Pressure 50 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.
Solution I (Normal)	50	22.0
Solution II (Extract) ...	47	22.0
	47	17.0
Normal (I)	47	17.0
	47	18.5
Extract (II)	44	18.0
	42	13.0
Normal (I)	42	19.0
Extract (II)	41	19.0
	41	15.5
Normal (I)	39	15.5
	39	19.0
Extract (II)	39	19.0
	39	16.0
Normal (I)	38	16.0
	38	17.0
Extract (II)	38	17.0
	38	13.0

Experiment III. Action of more dilute extract of tetanized muscle, in which the normal blood flow was maintained throughout the period of tetanization, compared with extract of resting muscle on the isolated cat's heart. First cat anesthetized, cord exposed, cut, and stimulated for forty-five minutes. Thigh muscles removed and placed in shaking machine along with an extract of resting muscle obtained from a second cat, which was anesthetized and bled to death. These were kept in the shaking machine for four hours, and at the end of this time a third cat was anesthetized, bled, and heart suspended. The solutions were made up as follows:

Solution I. 4000 cc. Locke's solution, 35 cc. blood of resting cat, 50 cc. extract of resting muscle.

Solution II. 4000 cc. Locke's solution, 35 cc. blood of resting cat, 50 cc. extract of blood from tetanized muscle.

Temperature of perfusion 35.5° C. Pressure 47 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.
Solution I (Normal) ...	67	13.5
Solution II (Tetanized).	65	13.0
	66	15.0
Normal (I)	66	15.0
	66	15.0
Tetanized (II)	64	16.5
	63	18.0
Normal (I)	62	17.0
	63	16.5
Tetanized (II)	62	17.5
	59	16.0
Normal (I)	57	16.0
	52	13.5

Experiment IV. This experiment was an exact duplication of Experiment III, except that the extract of resting and fatigued muscles were of

still lower strength: 1 cc. of the extract to 160 cc. of the Locke's blood perfusion solution. The muscles from which the fatigue extract was made were tetanized for one hour. The two perfusion solutions were made up as follows:

Solution I. 4000 cc. Locke's solution, 27 cc. blood of resting cat, 25 cc. extract of resting muscle.

Solution II. 4000 cc. Locke's solution, 27 cc. blood of resting cat, 25 cc. extract of tetanized muscle.

Temperature of perfusion 35.5° C. Pressure 56 mm. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.	Outflow in ccm. in 30 sec.
Solution I (Normal) ...	80	18.5	
Solution II (Tetanized).	75	18.0	
	72	23.5	27.0
	68	32.5	
Normal (I)	65	32.5	
	63	29.0	17.0
	63	28.0	16.0
Tetanized (II)	63	28.0	
	63	31.5	19.5
	62	31.5	20.0
Normal (I)	62	31.5	
	59	29.0	16.0
	62	26.5	15.0

Experiment V. Effect of blood from tetanized animal on the isolated heart. First cat was anesthetized, spinal cord cut, and distal end stimulated for one and one-half hours. The animal was then bled, the blood defibrinated and added to Locke's solution. A second cat was then anesthetized, bled, and the blood defibrinated and added in same amounts to the control solution. The heart from this cat was suspended and the two solutions tested. The solutions were made up as follows:

Solution I. 3000 cc. Locke's solution, 37½ cc. blood from resting cat.

Solution II. 3000 cc. Locke's solution, 37½ cc. blood from cat in which muscles of posterior limbs had been tetanized for one and one-half hours.

Temperature of perfusion 35.5° C. Pressure 50 mm. of mercury. The results are given in the following table:

	Heart rate in 30 sec.	Amplitude in mm.
Solution I (Normal)	102	14.0
Solution II (Tetanized) .	99	14.0
	98	17.0
	96	19.0
Normal (I)	95	18.5
	99	17.5
	93	17.0
Tetanized (II)	92	18.5
	91	21.5
	89	20.0

Experiment VI. This experiment was identical with the preceding in procedure and results. The cord was stimulated in the tetanized animal for one hour and forty minutes and 50 cc. of blood from each animal was employed.

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CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XI. The Cause of the Polyphagia in Pancreatic Diabetes

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ONE of the striking symptoms of the diabetes mellitus induced in dogs by the complete removal of the pancreas is the voracity which these animals exhibit, especially during the terminal stages of the disease. Reduced to mere skeletons of their former selves by a rapid and progressive emaciation, their dry skin bearing indolent ulcers resulting from slight scratches, with eyes almost closed with a purulent conjunctival discharge, such animals will eat ravenously. In this extreme cachetic condition which precedes their death, when they are entirely indifferent to their surroundings and lie in their cages almost too weak to rise, they will liven up at the sight and smell of food and will muster up all their strength in an endeavor to get at the food and devour it. It is, therefore, not uncommon to find their stomachs at autopsy filled with food ingested but a few hours previously. Such dogs have been known to eat their own feces even when provided with food which for a normal animal would be an abundant day's ration.

A similar polyphagia has been described in man as occurring occasionally during the course of diabetes mellitus or marasmus arising from other causes. In a recent article on diabetes in early infancy Knox[1] mentions hunger among the more common symptoms of the disease.

An animal, however, exhibiting a comparable decrepid condition but of different etiology (pneumonia, parathyroid tetany, distemper), would certainly refuse food.

Does, then, an animal dying from pancreatic diabetes eat because it is *hungry?* Or does this polyphagia result from some

[1] Knox: Bull. Johns Hopkins Hospital, Sept., xxiv, No. 271, 1913.

perverted appetite induced by the diabetic condition? In other words, is the voracity a result of true hunger pains brought on by real hunger contractions?

Methods

Two female dogs were used. The modified Frank's gastrostomy described in a previous paper [1] provided fistulous openings for the insertion of the rubber balloon recording changes in the intragastric pressure. The records of the movements of the empty stomach (hunger contractions) were taken as previously reported. After taking daily records of the movement of the empty stomach in the normal animal the entire pancreas (Dog I) or the pancreatic graft (Dog II) was removed and daily records again taken from the empty stomach while the animal was succumbing to the effects produced by the complete pancreatectomy.

Results

Dog I. Small fox terrier. Gastrostomy Nov. 6, 1912. Uneventful recovery. Contractions of the empty stomach exhibited the type described recently as type I.

Dog I. Figure 1. Nov. 28, 1912. About two-thirds the original size. Type I contractions — the type of contraction characteristic for this animal before the onset of pancreatic diabetes. Horizontal line represents 0 mm. bromoform pressure.

On Nov. 23, 1912, supposedly complete pancreatectomy.

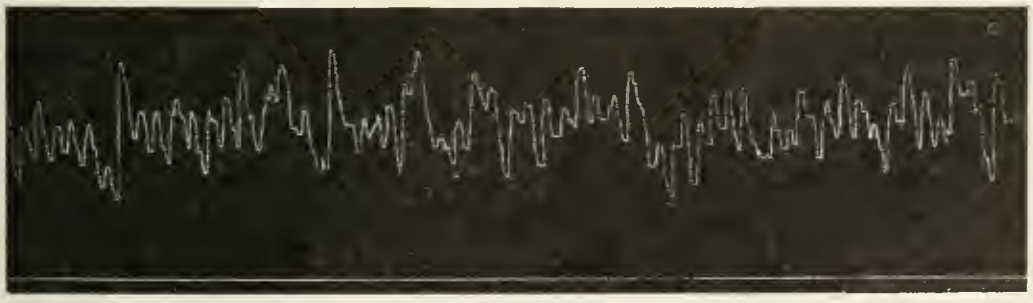
On Nov. 27, 1912, the animal had recovered from the effects of this severe operation. The hunger contractions conformed to the type

[1] Carlson: this Journal, 1913, vol. xxxii, p. 369.

described as type I and there was no change during the succeeding days (Nov. 28–30 inclusive). Figure 1 — An examination of the urine revealed the absence of sugar. The animal was, therefore,

Dog I. Figure 2. Jan. 7, 1913. About two-thirds the original size. Character of the stomach contractions after pancreatic diabetes was well established; type II and III contractions superimposed on periods of marked tetany. Plain horizontal line represents 0 mm. bromoform pressure.

used for the study of another problem until the Christmas holidays. On Jan. 4, 1913, it was noticed that the dog ate ravenously, but was in an extremely emaciated condition. The skin was dry; the dog had the mange; there were multiple small wounds about the toes and ears; and a purulent discharge issued from both eyes. The urine reduced Fehling's (2.49%) and fermented readily with



Dog I. Figure 3. Jan. 24, 1913. About four-sevenths the original size. Well marked type III contractions of the empty stomach. The horizontal line represents 0 mm. bromoform pressure.

yeast. From Jan. 6, 1913, on, daily tracings were taken from the stomach 24 hours after the last meal.

On Jan. 6, 7, and 11, type III contractions predominated, super-

imposed on periods of tetany lasting from 1 to 7 minutes (Fig. 2). From the 11th of January on, type III was the most prominent type of contraction, with occasional reversion to type II. On the 18th, 21st, and 24th of January the stomach was in tetany, with type III contractions most pronounced (Fig. 3). On these days the dog ate a good deal of lean meat, as is seen from the following table:

TABLE I

Date 1913	Body weight in kg.	Food in gm.	Food in gm. per kg. body weight
Jan. 6	5.600	350	62.5
Jan. 7	5.400	313	48.9
Jan. 12		345	61.6
Jan. 14	4.800	429	89.3
Jan. 15		460	95.8
Jan. 18	4.400	400	90.9
Jan. 24		248	56.3
Jan. 25	4.000	140	35.0
Average	4.84		67.5

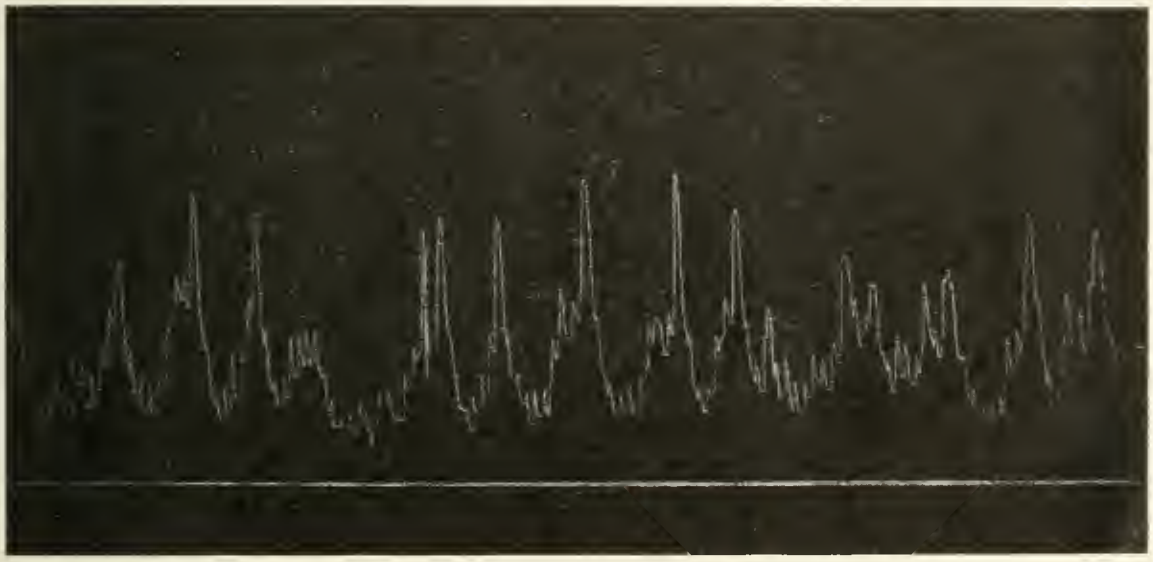
Jan. 25, 1913: Animal in a moribund condition. Rectal temperature 92.5° F. The dog was cold to touch. Could not stand unsupported. There were no marked movements of the stomach. The contractions were chiefly of type I variety. They were neither vigorous nor regular but nevertheless indicated slight hunger. At the end of the experiment the dog ate, with considerable difficulty, 140 gm. of lean meat. Immediate etherization. Stomach contained food just ingested. No macroscopic remnants of pancreas found. The 5 cc. urine found in the bladder did not reduce Fehling's solution.

The increased amount of food consumed by the animal towards the terminal stages of the disease (as high as 95.8 gm. meat per kg. body weight) compares favorably with a change in character and increased vigor of the hunger contractions.

Dog II. Fox terrier. Jan. 22, 1913: Pancreatectomy with pancreatic graft according to Hédon.[1] From Jan. 29, 1913, on, took daily records of the empty stomach 24 hours after the last meal. The types of contraction on the succeeding days were as follows:

Jan. 31, 1913: Types I and II (Fig. 4).
Feb. 1, 1913: Types I and II.
Feb. 2, 1913: Type III.
Feb. 3–Feb. 7 (inclusive): Type III.

Feb. 8, 1913: Removal of the subcutaneous pancreatic graft under light ether anesthesia. Wet weight of graft: 3 gm. Intense



Dog II. Figure 4. Jan. 31, 1913. Four-fifths the original size. Type II contractions indicating moderate hunger. The horizontal line represents 0 mm. bromoform pressure.

polyuria and glycosuria followed this operation immediately. (See Table II.)

Feb. 9–12 (inclusive): The contractions during this period conformed to the type described as type III. In spite of the fact that the stomach was in a high state of tonus, small tetany periods of several minutes' duration were noticed in addition.

Feb. 13–15 (inclusive): The contractions were the most pronounced (type III) seen in any dog under any condition up to that time. Figure 5 represents a portion of the tracing taken on Feb-

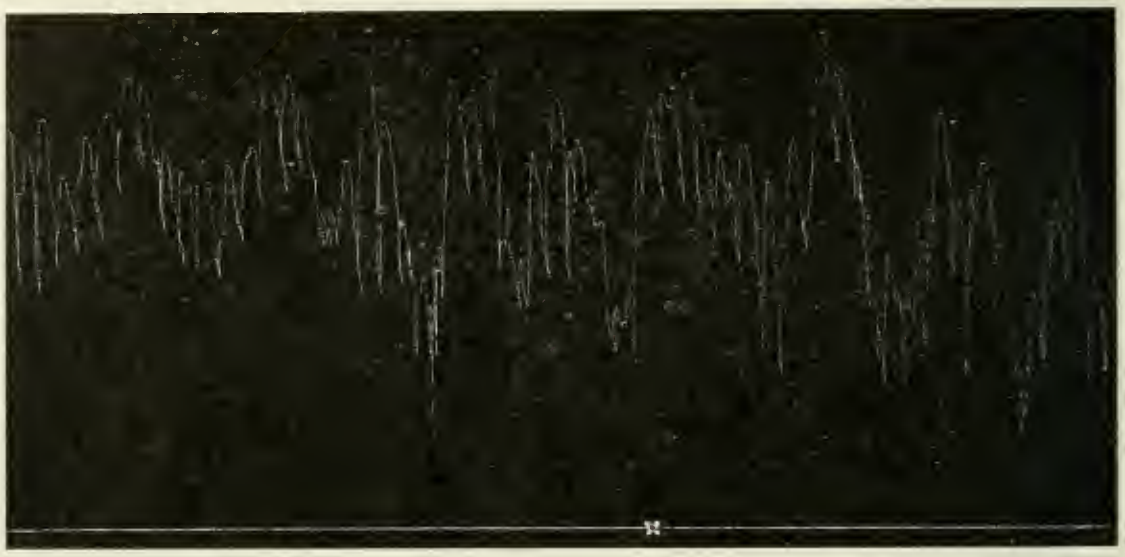
[1] Hédon: Archives internationales de physiologie, 1911, x, p. 350.

TABLE II

Dog II							
Date 1913	Body weight kg.	Food in gm.	Food in gm. per kg. body weight	Urine cc.	Sugar	Type of contractions	Remarks
Jan. 22							Pancreatectomy with graft
Jan. 27	5.440			270			
Jan. 28	5.100	264	51.7	180	1.92%		
Jan. 29	5.000			80			Gastrostomy
Jan. 30	4.835	165	34.3				
Jan. 31	4.900	161	32.8	150		I and II	
Feb. 1	4.700	165	35.1	60		I and II	
Feb. 2	4.500	158	35.1	40		III	
Feb. 3	4.500	187	41.5	75		III	
Feb. 4	4.280	395	91.8	35		III	

Feb. 5	4.300	259	60.2	40		III	
Feb. 6	4.200	207	49.2	40		III	
Feb. 7	4.100	280	68.2	55		III	
Feb. 8	4.100	206	50.	60		No record	Removal of graft
Feb. 9	4.100	150	36.5	175	5.31%	III	
Feb. 10	3.900	106	27.1	160	7.14%	III	
Feb. 11	3.700	137	37.0	83	5.55%	III	
Feb. 12	3.550	279	78.5	130	3.12%	III	
Feb. 13	3.500	201	57.4	70	6.25%	III	
Feb. 14	3.400	202	59.4	125	4.1%	III	
Feb. 15	3.240	105	32.4	90	2.5%	III	
Feb. 16	2.980	Refused food					
Feb. 17	2.980			15 cc. in bladder	Trace		Dead

ruary 13. The empty stomach is in incessant motion. In addition, there are seen short tetany periods. The strip of the tracing which is reproduced as Figure 5 represents the culmination of a tetany period lasting about 25 minutes. It will be noticed that at *X* the dog whined as if in pain. The tracings taken on the 14th and 15th of February are similar. On the 15th the dog could scarcely walk; was cold to the touch. Rectal temperature 97.6° F. As seen from Figure 6, hunger contractions were marked (type III).



Dog II. Figure 5. Feb. 13, 1913. Two-thirds the original size. The culmination of a tetany period in the diabetic animal lasting about 20 minutes. Smaller tetany periods are likewise shown. Thoughout a type III rhythm on a high tonus. At *X* dog whined as if in pain. Horizontal line represents 0 mm. bromoform pressure.

At the conclusion of the experiment the dog, with considerable difficulty, ate 105 gm. of meat.

Feb. 16–17: Dog could scarcely raise head. Rectal temperature 90.3° F. Obtained no contractions of the empty stomach. Dog refused food and drink. Was found dead on the morning of the 17th. Table II gives in detail the results of this experiment.

Discussion

The results obtained from the two dogs were so clear cut that further experimentation was considered unnecessary. Both dogs during pancreatic diabetes ate well — more than a normal dog of the same weight would eat. They continued to eat when too weak

to stand unsupported and when they were cold to the touch (rectal temperature 90.3–92.5° F.). There can be no question that they ate because they were *hungry;* for the voracity exhibited was the result of powerful contractions of the empty stomach. The contractions were at least as powerful and possibly more powerful than the contractions seen subsequently in normal dogs starved for 10 to 12 days. One cannot escape the opinion that dogs dying

Dog II. Figure. 6. Feb. 15, 1913. Two-thirds the original size. Tracing obtained from the empty stomach less than two days before death. Throughout type III contractions on a high tonus. Dog could scarcely walk. Ate 105 gm. meat — the last meal before death, which followed two days later. The bottom of the cut may be taken as the line representing 0 mm. bromoform pressure.

from pancreatic diabetes are animals in the most extreme state of inanition.

After the appearance of pancreatic diabetes, Dog I consumed on an average 67.5 gm. meat per kilo body weight, the extreme being 48.9 and 95.8 gm. (Table I). Dog II did not exhibit as great a voracity. Prior to the removal of the graft this dog ate daily on an average 48.8 gm. per kilo body weight. After glycosuria had been induced he consumed on an average 51.1 gm. per kilo body weight (Table II). This slight increase (1.3 gm.) is insignificant. From an examination of Table II it is apparent that Dog II, before the removal of the graft, was not a normal animal. It is true that removal of the graft (3 gm.) was followed by an intense glycosuria and polyuria which persisted till two days before death. In addition, the dog lost its playful disposition and entered into that

apathetic state so characteristic of dogs dying from the effects of pancreatic diabetes. On the other hand, the "normal" dog *was losing weight rapidly*, in spite of the fact that the dog *ate more meat* in gm. per kilo body weight than a normal dog. Three normal dogs whose average weight was 7.65 kg. (extremes: 6.2–8.52 kg.) ate daily during a period of 37 days on an average of 22.48 gm. of meat per kilo body weight (extremes: 16.51–28.05 gm.). Before removal of the pancreatic graft, Dog II ate daily 48.9 gm. meat per kilo body weight, more than twice the amount consumed by a normal animal. Owing to the presence of the small pancreatic graft only a transient glycosuria followed extirpation of the greater portion of the pancreas. However, two of the striking symptoms of pancreatic diabetes had already appeared; namely, rapid loss in weight and polyphagia. The polyphagia of pancreatic diabetes was, therefore, well developed before a permanent glycosuria was established. The latter hastened the exitus without affecting the polyphagia. This polyphagia resulted from the most intense *hunger* contractions ever observed in animals up to that time.

The great activity of the stomach in these otherwise decrepid animals was a striking phenomenon. It was the *smooth* musculature of the stomach which showed untiring activity at a time when the skeletal musculature of the body was exceedingly susceptible to rapid fatigue. In fact, the strength of the stomach contractions increased as the power of the voluntary musculature diminished; for the stomach was in incessant motion at a time when the dog was too weak to stand unsupported and could not chew its food without taking an occasional rest.

Résumé

A dog dying from pancreatic diabetes consumes more food per kilo body weight per day than does a normal animal. This polyphagia of pancreatic diabetes has been mentioned by most observers. It was not clear, however, whether the polyphagia resulted from a true sense of hunger or was a morbid desire or perverted appetite brought on by this diseased condition. But from the evidence presented in this paper it is certain that this polyphagia is the result of true hunger; for (*a*) the hunger contractions not

only persist after removal of the pancreas, but (*b*) become more intense with the progress of the disease, just as the voracity of the animal increases during the terminal stages of the disease. The animal dies in an extreme degree of inanition and eats ravenously because of the increased intensity of the gastric hunger contractions.

THE INFLUENCE OF THE RATE OF URINE FLOW ON THE SECRETION OF URIC ACID

By J. H. ROBERTSON

[*Department of Pharmacology, University of Toronto*]

THE paper published by Sharpe[1] last year from this laboratory indicated that even with the methods of urinary analysis which he employed, some light on the factors influencing the secretion of uric acid might be gained if hens, which have a urine twice or more as rich in that constituent as dogs or man, were used. At the suggestion of Professor Henderson this investigation was immediately undertaken.

Since this work was begun, the publication of Folin's new methods have made the problem even more approachable. The uric acid estimations in some of the preliminary experiments were made by Kowarski's modifications of the Hopkins' method, which was found to give accurate estimations, if the piperidin solution were standardized each time that it was employed, and if the titrations were made rapidly. An attempt was made to improve the method by using piperidin, a much less volatile base, but unfortunately no indicator could be found that gave a sufficiently sharp end-point to both this base and uric acid.

On the publication of the colorimetric method of Folin and Macallum,[2] it was tested and found to give satisfactory results; and as soon as the improved method of Folin and Denis[3] was published, it was also proved, and appearing satisfactory, was adopted. Difficulties were encountered with one or two cases of urine from dogs. In these the addition of the silver lactate reagent caused a dense precipitate, which turned black in from twenty to sixty seconds, and the amount of uric acid found was much less

[1] SHARPE: this Journal, 1912, xxxi, p. 75.

[2] FOLIN and MACALLUM: Journal of biological chemistry, 1912, xiii, p. 363.

[3] FOLIN and DENIS: Journal of biological chemistry, 1913, xiv, p. 95.

than that expected. Other samples to which larger amounts of the silver reagent were added gave equally bad results, and on estimating the amount of uric acid with the Folin-Macallum method, nearly six times as much uric acid was found as with the Folin-Denis method. The small amount of urine remaining in the first case was taken to Dr. Raper, to whom the author wishes to express his thanks for the assistance given on this and other occasions, and he suggested that the reaction might be due to thiosulphates. Various tests were made that indicated their presence, but the quantity of urine was too small to make a quantitative study. Dogs' urine, to which thiosulphates were added, gave a somewhat similar reaction. The amount of other salts present seemed also to influence the reaction.

An estimate of the amount of uric acid in the blood of hens was made in two cases. In Experiment 14, 6.16 mgm. were found in 100 gm. of blood, and in the other 5.15. The average reported by Folin and Denis[1] was 4.9. The higher result in these cases may be due to the fact that the animals had previously secreted a considerable amount of urine. In the blood of a dog, 0.67 mgm. was found in 100 gm., and in that of a cat 0.205, which agrees very closely with the amount found by Folin.

In the experiment illustrated by Figure 3 in Sharpe's paper, it seemed that injections of uric acid dissolved in piperazin caused a considerably greater secretion of urine than would have been expected from the same amount of piperazin alone, and this suggested that the excretion of uric acid was accompanied by a considerable loss of water. This is hardly what might be expected from a consideration of the histological picture presented by the work of those who have investigated the subject microscopically.[2] A brief review of these papers will make this clear.

Sauer injected into rabbits, which normally secrete very small amounts of uric acid, a solution of uric acid in piperazin. The in-

[1] Folin and Denis: Journal of biological chemistry, 1913, xiv, p. 29.

[2] See Erbstein and Nicolaier: Archiv für pathologische Anatomie, 1896, cxlvi, p. 377; Sauer: Archiv für mikroskopische Anatomie, 1899, liii, p. 218; Anten: Archives internationales de pharmacodynamie et therapie, 1901, viii, p. 455; Courmont and André: Journal de physiologie et pathologie générale, 1905, vii, p. 197; Todaro: Archives italiennes de biologie, 1902, xxxviii, p. 33.

jections are followed by a marked flow of urine and by the secretion of uric acid. The piperazin alone would cause a marked urine flow. The kidneys were examined fresh, and uric acid particles were described as appearing in the cells and lumina of the convoluted tubules, but none in the glomeruli or its capsule. The cells of the loop of Henle and of the collecting tubules were free from particles, but these were to be seen in their lumen. The fine particles were found only in the outer half of the cells, and the striated border appeared as if broken by their extrusion. To prove that the particles in the lumina of the lower tubules were due to washing down from above, some experiments were performed in which a part of the cortex was destroyed, and then the injection given; in the lower tubules of the destroyed area no particles were found, though the convoluted tubules were full of them.

Anten injected the kidneys of dogs from the renal artery with an ammoniacal silver chloride solution, the excess of which was washed out with saline, and the kidneys were then fixed in alcohol. He found the cells of the convoluted tubules and the wide ascending limb of Henle's loop filled with fine particles, but these occurred rarely in the glomerulus, and never in the space of Bowman's capsules, nor in the other capsules.

Courmont and André extended the observations of Anten to representatives of various vertebrate types. They fixed first, in an absolute alcohol, glacial acetic acid and chloroform mixture, and cut sections which they treated with hydrochinon and with silver nitrate. They made controls with ammoniacal silver solution. They found uric acid granules in the position described by the previous authors, save that they found them also in the cells of the descending limb of Henle in the dog. The position of the granules in the outer halves of the cells corresponded to the position of the so-called crystalloid vacuoles described by Gurwitsch. They thought that they were able to show some effect on the particles when they injected pilocarpine previously to removing the kidney.

Todaro describes uric acid particles collected in the cells of the kidney canals of tunicates and says that these are gradually carried to the surface and there excreted in a slimy mass.

Tribondeau [1] similarly describes how the contents of the vacu-

[1] Tribondeau: Comptes rendus de la Société biologique, 1901, liii, p. 1188.

oles in the kidney cells of snakes pass in the forms of drops through the striated border of the cells and appear in the lumen in clumps.

The experiments were first carried out on hens alone. The technique was the same as that described by Sharpe.[1] As was noted by him, marked variations in the rate of urine flow often occurred without assignable cause, though this may in part be explained as due to the changes in blood pressure, as a constant record of this factor was rendered difficult by the occurrence of marked rings of constriction in the exposed carotid arteries which at times made the manometer record of little value.

Protocols or curves illustrating them are given only of typical experiments, though many more, some 25 in all, were performed.

EXPERIMENT 3

HEN, WEIGHT 2 K., URETHANE AND ETHER

Time in min.	Cc. urine per min.	Mgm. uric acid per min.	Mgm. uric acid per cc.	Urine in cc.
32	2.50	4.15	1.66	7.5
36	2.35	3.61	1.54	9.5
42	1.61	2.19	1.36	9.7
50	1.31	1.87	1.43	10.5
62	0.76	0.988	1.30	3.8
68	3 cc. of a 5% solution of piperazin			
76	0.80	1.16	1.45	4.0
83	0.58	0.84	1.45	2.9
86	0.60	0.85	1.43	3.0
91	0.44	0.62	1.41	2.2
96	0.32	0.45	1.43	1.6
101	0.32	0.44	1.38	1.6
125	50 mgm. uric acid dissolved in 3 cc. 5% piperazin			
136	0.17	0.66	1.54	5.9
146	0.14	0.27	1.96	1.4
161	2 cc. 10% piperazin			

[1] SHARPE: *Loc. cit.*

174	0.12	0.26	2.17	2.9
204	2 cc. 10% piperazin			
224	0.078	0.15	1.96	3.9
224	3 cc. 20% Na_2So_4			
234	0.22	0.435	1.98	2.2
234	40 cc. Ringer's solution			
245	80 cc. Ringer's solution			
262	0.36	0.59	1.66	10.0
272	0.58	0.14	0.25	5.8

EXPERIMENT 6

ROOSTER, WEIGHT 3 K., URETHANE AND ETHER

Time in min.	Cc. urine per min.	Mgm. uric acid per min.	Mgm. uric acid per cc.	Cc. urine
9	0.84	1.20	1.43	7.6
15	1.10	2.09	1.90	6.6
25	20 mgm. caffeine sodium benzoate			
26	0.54	1.13	2.10	6.0
30	1.35	1.93	1.43	5.4
34	1.35	1.22	0.91	5.4
38	1.37	1.37	1.00	6.5
39	20 cc. Ringer's solution			
42	2.50	1.66	0.66	10.0
46	3.50	2.06	0.59	14.0
50	3.00	1.92	0.64	12.0
54	2.00	2.00	1.00	8.0
58	1.45	1.98	1.37	5.8
62	1.12	1.99	1.78	4.5
62	2 cc. 20% Na_2SO_4 solution			
70	0.88	1.81	2.06	7.0
78	0.64	1.38	2.17	5.1

78	2 cc. 20% Na_2SO_4 solution			
89	0.48	1.04	2.17	5.3
93	1.95	1.56	0.80	7.8
97	1.90	0.95	0.50	7.5
104	1.57	0.97	0.62	11.0
112	1.00	1.33	1.33	8.0
120	0.60	0.90	1.51	4.8
128	0.36	0.75	2.10	2.9
138	20 cc. Ringer's solution			
140	0.32	0.64	2.00	3.8
148	0.74	1.48	2.00	5.9
148	20 cc. Ringer's solution			
156	0.94	1.44	1.54	7.5
168	0.87	1.44	1.66	10.5
180	0.65	1.07	1.66	7.8
201	0.39	0.82	2.10	8.2
232	0.30	0.60	2.00	9.5
272	0.27	0.51	1.90	11.0
312	0.18	0.34	1.90	7.2
366	0.10	0.26	2.66	5.8

If in the protocols the flow of urine per minute be compared with the output of uric acid, a very striking general parallelism may be noted. Increased output of fluid is accompanied by increase in uric acid. This was quite striking in No. 14, which is shown in the form of a curve (Fig. 1). In other cases, while the parallelism is true in a broad sense, it is not true in detail; for example, in Experiment 6, between the 50th and 65th minutes the uric acid per minute remains high, while the flow is falling off very rapidly.

On comparing the curves of urine flow per minute and that of uric acid per cubic centimetre of urine, the latter is in general the obverse of the former; but this contrast is by no means so exact as

is the parallelism between urine flow and uric acid output per minute. For example, in Experiment 3 there is at first a fall in the uric acid accompanying the fall in urine flow. This fall of uric acid comes to an end about the 62d minute, while the fall in water output continues. Indeed, the succeeding portion of the curve would suggest that the injection of piperazin had led to a special excretion

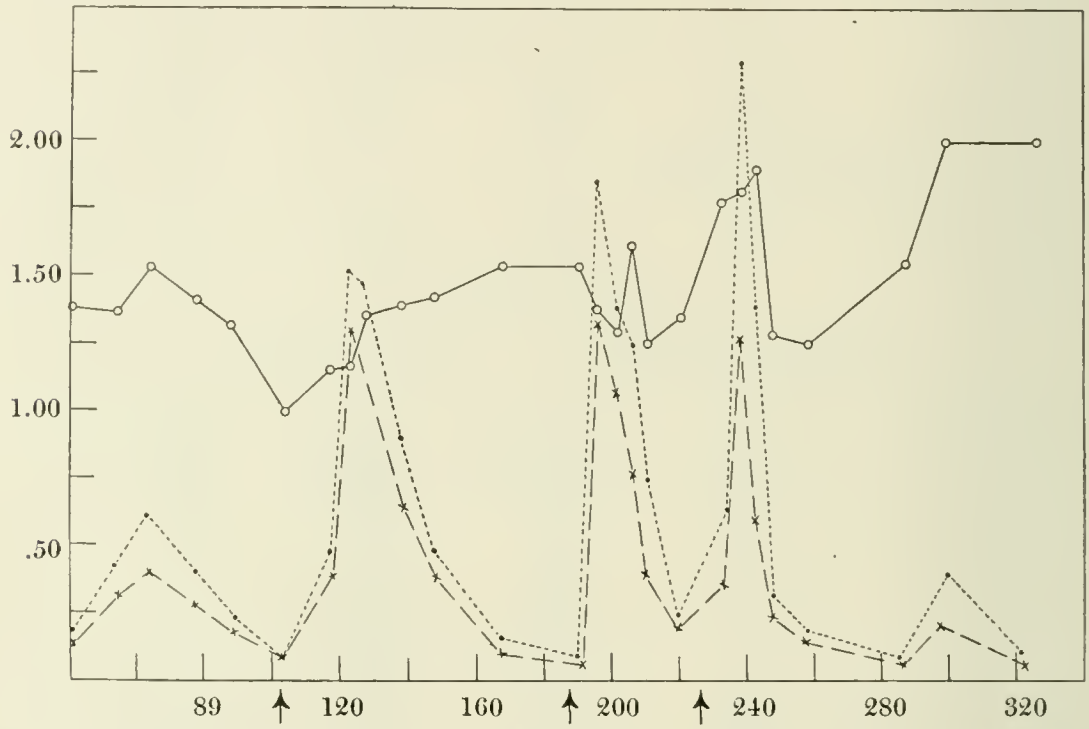


FIGURE 1. — Experiment 14. Increased output of urine is accompanied by increase in uric acid. The full line shows milligrams of uric acid per cubic centimetre of urine. The dotted line shows milligrams of uric acid per minute. The dashes show cubic centimetres of urine per minute. The abscissae mark time in 20 minute intervals. The ordinates mark milligrams of uric acid per minute and cubic centimetres of urine per minute respectively. The arrows mark adrenalin and the asterisk marks caffeine.

of uric acid unaccompanied by much water. In other experiments with this drug such results were not so strikingly obtained, and no conclusion has been reached on this point as yet. Sharpe had noticed that when the blood pressure was low and urine secretion tardy, an injection of adrenalin often produced a considerable diuresis; and in consequence, in Experiment 14 (Fig. 1), three injections of adrenalin were given. It will be noted that the increase in flow of urine is surpassed by the output of uric acid per minute, and that the curve of uric acid per cubic centimetre does not fall distinctly with the increase of urine flow, and indeed, after the third injection, rises in a definitely independent fashion, which

again suggests a possibly specific excretory effect. This result might, perhaps, be more simply explained by the marked changes in blood distribution produced by the cardiac and vascular effects of the drug.

In the experiments reported upon in this paper, changes in the rate of urine flow succeeded the injection of normal saline (Ringer's solution), caffeine, hypertonic sodium sulphate, piperazin, adrenalin, 2-phenyl-chinolin-4-carbonic acid (atrophan), potassium nitrate (2% solution), and barium chloride, and characteristically with all these, the rate of uric acid production varied with the urine flow. It will be readily granted that all these drugs can hardly produce the effects observed directly, but probably acted indirectly by influencing the blood flow through the gland.

Although the blood flow through the kidney in general runs parallel with the urine production, this is not true under all conditions; as, for example, in experiments reported by Barcroft and Brodie[1] and by Loewi.[2] Also the output of uric acid might well be influenced by the blood flow through the organ in a manner quite different from the urine production, and in consequence some experiments were undertaken in which this factor was also recorded.

For this purpose the anatomical relations of the kidney in hens made their employment impossible, and large dogs were used. It was imperative that any method employed to measure the blood flow should be one that produced as little disturbance of metabolism and circulation as possible. The most exact method of measurement is that described by Barcroft and Brodie,[3] in which the venous flow is measured by allowing it to run along a graduated glass tube inserted into the vena cava below the kidney. This method, however, owing to the obstruction of the cava alone, quite apart from the complete evisceration which these workers employed, made the method unavailable for our purpose. Plethysmography alone, as shown by Loewi,[4] cannot be entirely relied

[1] Barcroft and Brodie: Journal of physiology, 1905, xxxiii, p. 67.

[2] Loewi: Archiv für experimentelle pathologie und pharmacologie, 1905, liii, p. 16.

[3] Barcroft and Brodie: Journal of physiology, 1904, xxxii, p. 18.

[4] Loewi: *Loc. cit.*

upon. The method employed was that described by Brodie and Russell,[1] in which the plethysmograph containing the kidney is connected with a delicate recorder writing upon a rapidly revolving drum, and the rate of flow measured by the rate of dilatation of the organ, when the kidney vein is temporarily constricted. Results of a typical experiment of this type are shown in the protocol for Experiment 21.

EXPERIMENT 21

Dog, Male, Weight 20 k., Morphine, Ether

Time in min.	Cc. urine per min.	Mgm. uric acid per min.	Mgm. uric acid per cc.	Amount urine cc.	Time to dilate kidney
12					1.40
26					1.65
33	0.1	0.1	1.0	3.3	
40					1.75
58	0.09	0.09	1.0	2.3	
59	Pituitary extr. 1 cc.				
60					1.45
68					1.00
84	0.09	0.086	0.96	2.3	
88					1.55
94	0.23	0.24	1.05	2.3	
96					1.70
98	Saline				
101	0.36	0.30	0.85	2.5	
105	0.80	0.37	0.47	3.2	1.10
109	$BaCl_2$				1.18
110	0.44	0.18	0.41	2.2	
112					1.98
132					1.60
134	0.09	0.06	0.67	2.2	1.62

[1] Brodie and Russell: Journal of physiology, 1905, xxxii, proc. xlvii.

150					1.85
152	0.16	0.15	0.96	3.0	
160					1.80
161	Caffeine 2% solution				
162					1.55
166	0.21	0.225	0.75	3.0	
170					1.25
180					1.95
182	0.26	0.25	0.96	4.2	
196	$BaCl_2$				1.98
197	0.19	0.18	0.96	2.8	
201					2.40
206					1.90
213	0.14	0.14	1.0	2.3	1.75
214	N_2SO_4				
220	0.77	0.53	0.7	5.4	1.20
224	1.35	0.27	0.20	5.4	
230					1.90
231	0.94	0.20	0.23	6.6	
238					2.00

In this experiment the time is calculated during which the kidney would be dilated by an arbitrary amount, which was approximately 2.5 cc., as only comparative figures were required. In this, as in the other experiments of this type, a general parallelism between the rate of flow of urine and uric acid is evident, and in general the rate of blood flow increased with increasing urine production. In none of the experiments, however, were we successful in producing a change in uric acid secretion which was sufficiently independent of urine flow to suggest any specific effect of the drugs injected; nor could any dependence of the rate of uric acid secretion on blood flow alone be established, as in all cases the variation in urine production paralleled the changes in blood flow.

Summary

In spite of the accuracy of the methods introduced by Folin for the determination of uric acid, the experiments reported above show clearly the difficulty in determining whether the excretion of uric acid by the kidney is a specific process of secretion accompanied by a considerable quantity or by very little water. Nor have these experiments been successful in definitely establishing whether increased water excretion or the change in the blood flow through the gland is primarily responsible for the parallelism between the increase in urine flow and uric acid excretion. Certain of the experiments indicate that the uric acid excretion may vary independently of the urine flow, and that increased uric acid excretion does not necessarily lead to much increase in the amount of urine. It is hoped that further experimentation will give a more definite result.

STUDIES IN FATIGUE

III. The Fatigue Threshold as Affected by Adrenalin and by Increased Arterial Pressure

By CHARLES M. GRUBER

[*From the Laboratory of Physiology in the Harvard Medical School*]

IN a previous paper I showed that fatigue increases the normal threshold stimulus, on an average, between 100 and 200 per cent, and may increase it more than 600 per cent, whether taken from the normal muscle directly or from the nerve-muscle; that a subsequent rest varying from 15 minutes to two hours restores the muscle and nerve-muscle to their original threshold irritability, and that the time required for restoration depends upon the duration of the fatigue and the condition of the animal.[1]

That the removal of the suprarenal capsules has a marked effect upon the efficiency of striated muscle has long been known. The first conclusive evidence showing that adrenal extract has a bettering effect on the muscular contraction was given by Oliver and Schäfer.[2] After injecting the extract subcutaneously into a frog and then excising the gastrocnemius muscle, these authors observed a curve of contraction which was higher and longer than that of the corresponding muscle not exposed to the extract. A similar prolongation of the muscle curve was observed after the extract was injected intravenously into a dog. Dessy and Grandis claimed that adrenal extract produces a beneficial effect on fatigued muscle either when injected subcutaneously into a salamander or when added to the solution in which the isolated muscle is contracting.[3] Radwánska found in frogs that the beneficial action of adrenalin is far greater when the muscle is stimulated through its

[1] Gruber: this Journal, 1913, xxxii, p. 438.

[2] Oliver and Schäfer: Journal of physiology, 1895, xviii, p. 263.

[3] Dessy and Grandis: Archives italiennes de biologie, 1904, xli, p. 231.

nerve than when stimulated directly.[1] Further evidence tending toward the same conclusion was offered by Panella, who observed this phenomenon of reinforced activity in striated muscle in heterothermic animals, and also in homothermic animals the conditions of which were rendered by experimental procedures like those of the heterothermic.[2] Cannon and Nice more recently demonstrated that adrenalin injected in small doses or secreted during splanchnic stimulation causes an improvement in the activity of fatigued muscle.[3] In my first paper of this series I confirmed their results and showed, in addition, the quantitative relation between arterial pressure and the height of the fatigue curve. In conclusion I referred to this statement made by Cannon and Nice: "The observations here recorded, however, indicate that adrenalin may operate favorably in making more effective the nervous impulses delivered to fatigued muscles." [4]

The question whether or not this increase in muscular efficiency after an injection of a small dose of adrenalin, or after splanchnic stimulation with or without the adrenal glands intact, is the result of lowering the threshold irritability has been the subject of this investigation.

The Method

In some cases the animals (cats) were anesthetized with urethane (2 gm. per kilo body weight by stomach), in others they were decerebrated. The nerve-muscle preparation was the tibialis anticus muscle and the nerve supplying it the peroneus communis. The stimulating current for fatigue was a maximal break induction shock obtained from a vulcanite disc interrupter. The rate of stimulation was 120 or 240 per minute. The rate was kept uniform throughout each experiment. Threshold stimuli were determined by the Martin method, in which the threshold is calculated in β units.[5]

[1] Radwánska: Anzeiger der Akademie, Krakau, 1910, pp. 728–736. Reviewed in Centralblatt für Biochemie und Biophysik, 1911, xi, p. 467.

[2] Panella: Archives italiennes de biologie, 1907, xlviii, p. 462.

[3] Cannon and Nice: this Journal, 1913, xxxii, p. 49.

[4] Gruber: this Journal, 1913, xxxii, p. 221; Cannon and Nice: *Loc. cit.*, p. 59.

[5] Martin: Measurement of Induction Shocks, New York, 1912, pp. 71–93. For detailed description of the method employed in this work see Gruber: this Journal, 1913, xxxii, p. 438.

A mercury manometer was employed to record the arterial pressure, which was taken, in every case, from a cannula in the right carotid artery. When adrenalin was injected or the splanchnic nerves stimulated, the blood pressure was allowed to return to normal before the threshold stimulus was determined.

The method for stimulating the left splanchnic nerves was that of Cannon and Nice.[1]

Through a cannula placed in the left external jugular vein the adrenalin was injected *slowly*, usually in doses of 0.1 cc. of a 1:100,000 solution, and never in doses exceeding 0.5 cc. Through another cannula placed in the right external jugular vein amylnitrite was, in some experiments, injected in doses sufficiently large to cause a marked fall in blood pressure.

Experiments were also performed in which the hind leg was irrigated, at a constant pressure of 95 mm. of mercury, through cannulas in the external iliac artery and vein. The medium for irrigation was a warm (38.5–40° C.) Ringer's solution. The adrenalin was injected into the running solution close to the arterial cannula.

In an attempt to determine whether the action of adrenalin is on the muscle or on the nerve-endings or both, a number of experiments were performed on animals in which a section (2 cm. long) of the left peroneus communis nerve was removed aseptically 6 to 21 days previous to the experiment.

The Effect of Adrenalin upon the Fatigue Threshold

The normal threshold stimulus of the peroneus communis nerve varied in the animals used from 0.35 to 5.45 β units, with an average in nine experiments of 1.3. (See Table I.) This average is the same as that found by E. L. Porter for the radial nerve of the spinal cat, and as that cited in an earlier paper of this series for the peroneus communis of the decerebrate cat.[2] For the tibialis anticus muscle, in which the nerve-endings were intact, the threshold varied from 6.75 to 49.3 β units, with an average in the nine

[1] Cannon and Nice: *Loc. cit.*, p. 47.

[2] E. L. Porter: this Journal, 1912, xxi, p. 149; Gruber: this Journal, 1913, xxxii, p. 443.

TABLE I

THE EFFECT OF ADRENALIN UPON THE FATIGUE THRESHOLD STIMULUS OF THE TIBIALIS ANTICUS IN DECEREBRATE CATS. MEASUREMENTS TAKEN BY THE MARTIN METHOD FROM (I) THE PERONEUS COMMUNIS NERVE AND (II) THE MUSCLE DIRECTLY

I									II				
Length of Fatigue	Rate of Stimulation	Initial Tension of Spring	Normal β	Fatigue β	Fatigue β after Adrenalin	Increase in per cent	Recovery of the Threshold in per cent	Number of cc. of Adrenalin injected	Normal β	Fatigue β	Fatigue β after Adrenalin	Increase in per cent	Recovery of the Threshold in per cent
2 hr. 25 min.	120	200	1.25	4.23	0.84	238	112	0.1	20.67	74.5	58.5	261	36
1 hr.	120	120	0.62	0.89	0.79	43	37	0.1	30.0	51.6	38.0	72	62
46 min.....	120	200	0.45	0.82	0.74	82	21	0.5	24.9	84.4	70.2	239	24
1 hr.	120	120	0.67	1.0	0.87	49	39	0.1	10.0	30.6	18.0	206	61
1 hr.	240	120	1.79	2.27	2.07	27	42	0.3	14.7	47.0	21.7	220	78
10 min.....	120	120	0.62	0.79	0.59	27	118	0.6	30.0	130.0	101.0	334	29
1 hr.	120	120	0.68	0.88	0.54	29	170	0.2	6.75	20.3	6.5	201	101
15 min.....	120	120	0.35	0.65	0.4	86	83	0.1	13.0	21.1	17.8	62	40
[1]4 hr.	120	200	[1]5.45	17.9	9.55	229	67	0.1	49.3	76.7	50.2	56	91
Average			1.3	3.3	1.8	154	75		22.2	59.6	42.4	169	46

[1] Urethane anesthesia.

experiments of 22.2. This is slightly higher than that cited for this same muscle in the paper mentioned above. By fatigue the threshold of the nerve-muscle was increased from an average of 1.3 to an average of 3.3 β units, an increase of 154 per cent. The muscle increased from an average of 22.2 to an average of 59.6, an increase of 169 per cent. (See Table I.) After an injection of 0.1 to 0.5 cc. of adrenalin (1:100,000) the fatigue threshold was decreased within five minutes in the nerve-muscle from an average β of 3.3 to 1.8, a recovery of 75 per cent, and in the muscle from an average β of 59.6 to 42.4, a recovery of 46 per cent. (See Table I.)[1] To prove that this effect of adrenalin is a *counteraction of fatigue*, I determined the threshold stimulus for muscle and nerve-muscle in non-fatigued animals before and after adrenalin injection. I found that in these cases no lowering of threshold occurred, a result in marked contrast with the pronounced and prompt lowering induced in fatigued muscles by this agent.

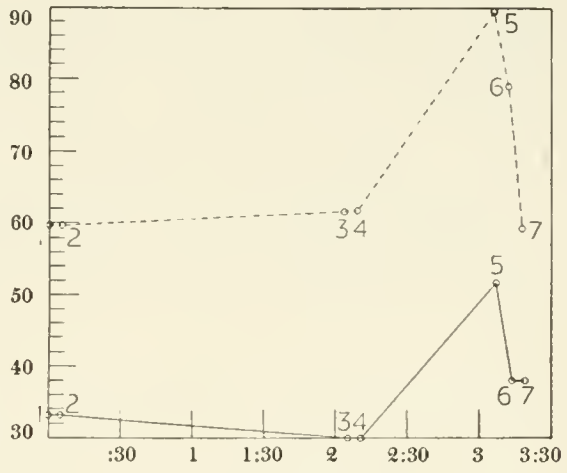


FIGURE 1.—A curve plotted from the data of one experiment. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The nerve-muscle curve is magnified 100 times; that of the muscle is normal.

(1) Normal threshold stimulus. (2) Threshold five minutes after an intravenous injection of 0.1 cc. of adrenalin (1:100,000) without previous fatigue. (3) Threshold after a rest of two hours. (4) Threshold five minutes after an injection of 0.2 cc. of adrenalin (1:100,000) without previous fatigue. (5) Threshold after one hour's fatigue. The muscle contracted 120 times per minute against a spring having an initial tension of 120 gm. (6) Threshold five minutes after an injection (0.1 cc.) of adrenalin (1:100,000). (7) Threshold five minutes after another injection of adrenalin (0.5 cc. of a 1:100,000 solution).

Figs. 1 and 2, plotted from the data of two of the experiments, show the relative heights of the threshold before and after an injection of adrenalin. The two readings of the threshold, one from the nerve supplying the muscle,

[1] The fatigue thresholds here cited do not always indicate the highest level reached. In some cases the reading was made after a period of rest. But this gives an indication of the action of adrenalin.

the other from the muscle directly, served to show that there was no fault in the electrodes. The continuous line in the curve represents the threshold (in β units) of the muscle, the broken line that of the nerve-muscle. The threshold of the nerve-muscle is magnified 100 times in Fig. 1 and 10 times in Fig. 2. In Fig. 1 (at 2 and 4) the threshold was taken after an intravenous injection of 0.1 and 0.2 cc. of adrenalin respectively.

These examples show that adrenalin does not affect the threshold of the normal non-fatigued muscle when taken either from the

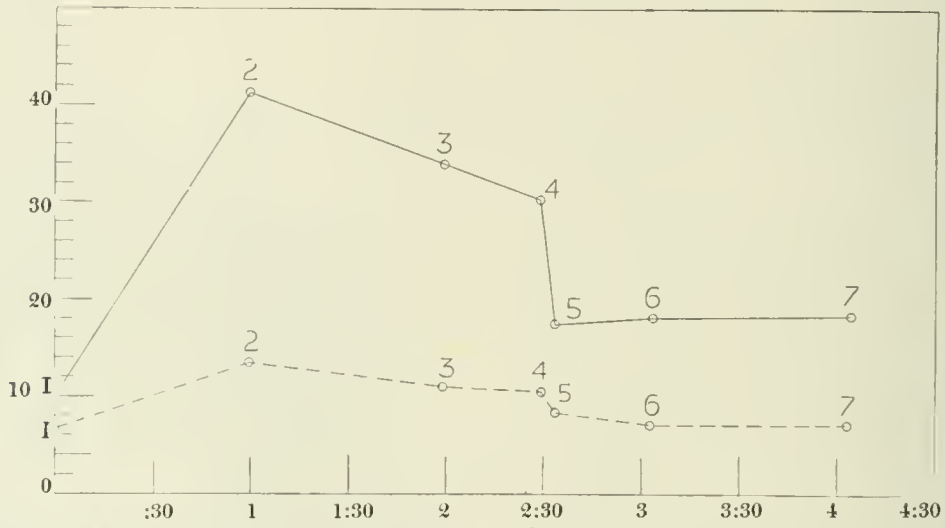


FIGURE 2. — A curve plotted from the data of one experiment. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The curve of the nerve-muscle is magnified ten times; that of the muscle is normal.

(1) Normal threshold stimulus. (2) The threshold after one hour's fatigue. The muscle contracted 120 times per minute against a spring having an initial tension of 120 gm. (3 and 4) Thresholds after rest; after 60 minutes (3), and after 90 minutes (4). (5) Threshold five minutes after an injection of adrenalin (0.1 cc. of a 1:100,000 solution). (6 and 7) Thresholds after rest; after 60 minutes (6), and after 90 minutes (7).

muscle directly or from the nerve-muscle. In Fig. 1 (at 3) the threshold was taken after two hours' rest. This confirms E. L. Porter's observation that the threshold may remain constant for a very long time when left in a state of rest.

In Fig. 1 the normal threshold stimulus was increased by fatigue (at 5) — the muscle pulling 120 times a minute for one hour on a spring having an initial tension of 120 gm. — from 30.0 to 51.6 β units, an increase of 72 per cent; and in the nerve-muscle from 0.62 to 0.89 β units, an increase of 46 per cent. In

Fig. 1 the threshold (at 6) was taken five minutes after injecting 0.1 cc. of adrenalin (1:100,000). The threshold of the muscle was lowered from 51.6 to 38.0 β units, a recovery of 62 per cent; that of the nerve-muscle from 0.89 to 0.79 β units, a recovery of 37 per cent. After another injection of 0.5 cc. of adrenalin the thresholds (at 7) were taken; that of the nerve-muscle dropped to normal — 0.59 β units — a recovery of 100 per cent, and that of the muscle remained unaltered — 26 per cent above its normal threshold.[1]

In Fig. 2 the threshold (at 5) was taken five minutes after an injection of 0.1 cc. of adrenalin. The drop here was as large as that shown in Fig. 1. The threshold taken from the muscle directly was lowered from 30.6 to 18 β units, a recovery of 61 per cent; the nerve-muscle from 1.08 to 0.87 β units, a recovery of 51 per cent. That this sudden decrease cannot be due to rest is shown in the same figure (at 3 and 4). These readings were made after 60 and 90 minutes' rest respectively. The sharp decline in the curve (at 5) indicates quite distinctly the influence of adrenalin upon fatigue threshold irritability.

Splanchnic Stimulation

The average normal threshold taken from the peroneus communis nerve in a series of eleven experiments was 3.4 β units, and directly from the tibialis anticus muscle, in which the nerve-endings were intact, it was 29 β units. The former average threshold was increased by fatigue to 5.96, an increase of 75 per cent, and the latter to 58.3, an increase of 101 per cent. Stimulation of the left splanchnic nerves, in some cases for 30 seconds, in others for one minute, reduced this average fatigue threshold in the nerve-muscle from 5.96 to 4.9, a recovery of 41 per cent, and in the muscle from 85.3 to 40.4 β units, a recovery of 62 per cent. (See Table II, *A*.)

Fig. 3 is a curve plotted from the data of one of the experiments, showing the effect of splanchnic stimulation upon the threshold stimulus. The broken line is the curve of the nerve-muscle,

[1] This discrepancy may be due to variation in placing the electrodes in the muscle. The results from readings on the nerve are more likely to be uniform and reliable.

TABLE II

THE EFFECT OF LEFT SPLANCHNIC STIMULATION UPON THE FATIGUE THRESHOLD STIMULUS OF THE TIBIALIS ANTICUS MUSCLE IN CATS IN URETHANE ANESTHESIA. MEASUREMENTS TAKEN BY THE MARTIN METHOD FROM (I) THE PERONEUS COMMUNIS NERVE AND (II) THE MUSCLE DIRECTLY. (*A*) THE ADRENAL GLANDS ARE INTACT AND (*B*) THE LEFT OR BOTH ADRENAL GLANDS ARE TIED OFF.

	I									II				
	Length of Fatigue	Rate of Stimulation	Initial Tension of Spring	Normal β	Fatigue β	Fatigue β after Splanchnic Stimulation	Increase in per cent	Recovery of the Threshold in per cent	Length of Splanchnic Stimulation in seconds	Normal β	Fatigue β	Fatigue β after Splanchnic Stimulation	Increase in per cent	Recovery of the Threshold in per cent
A	15 min.	120	120	1.79	2.9	2.36	62	48	30	22.3	51.8	24.2	115	94
	1 hr.	120	120	2.36	2.88	2.1	22	120	30	19.3	30.4	27.2	57	31
	15 min.....	120	120	2.1	2.4	2.1	14	100	60	30.2	39.1	37.0	31	23
	1 hr.	120	120	1.1	1.65	1.12	50	91	30	32.1	70.2	43.7	119	69
	15 min.....	120	120	1.79	2.1	1.76	17	109	60	12.5	21.8	16.3	74	59
	45 min.	240	120	1.45	2.05	1.46	41	98	30	12.53	39.0	27.0	211	45
	5 min.....	240	120	1.35	1.6	1.41	19	54	60	16.4	30.6	18.6	86	83
	1 hr.	240	150	2.5	6.8	3.8	170	70	60	62.45	131.0	95.4	110	52

	[1] 1 hr.	240	150	6.9	11.99	10.8	74	23	60	38.8	118.5	71.6	212	120
	[1] 1 hr.	240	150	7.74	14.9	12.7	93	30	60	66.9	73.0	67.0	9	98
	[1] 30 min.. . . .	240	150	7.7	16.25	14.3	111	23	60	23.8	42.1	35.7	77	35
	15 min.	120	120						30	11.3	52.5	21.3	365	75
	Average			3.4	5.96	4.9	75	41		29.0	58.3	40.4	101	62
B	3 hr.	240	120	1.4	1.53	1.47	9	46	30	16.4	39.0	33.0	137	20
	1 hr. 15 min.	240	150	1.15	1.75	1.53	52	36	60	32.7	71.3	53.1	118	47
	1 hr. 30 min.	240	120	2.95	3.24	2.96	10	96	60	23.8	29.1	23.8	22	100
	7 min.	240	120	0.34	0.38	0.36	12	50	30	25.7	33.0	27.9	28	69
	1 hr. 30 min.	240	120	1.79	2.3	2.1	10	39	60					
	2 hr.	240	120	1.15	1.61	1.41	40	42	30					
	10 min.	240	120	1.15	1.47	1.37	27	31	60					
	Average			1.4	1.75	1.6	25	42		24.6	43.1	34.5	75	46

[1] Both splanchnic nerves cut before fatigue.

the continuous line that of the normal muscle expressed in β units. The threshold of the nerve-muscle is magnified ten times. In Fig. 3 the threshold (at 2) was taken after the muscle was fatigued through its nerve for one hour, pulling 120 times a minute against a spring having an initial tension of 120 gm. At the end of this period of fatigue the preparation rested five minutes and then a reading was taken (at 3). The left splanchnic nerves were stimulated for 30 seconds, and after a wait of three minutes the thresholds were taken again (at 4). The threshold of the muscle decreased from 70.2 to 43.7 β units, a recovery of 69 per cent, and from 1.65 to 1.12 β units, a recovery of 96 per cent, in the nerve-muscle. This shows clearly that the adrenalin secreted, or the increase in blood pressure, or the two together lowered the fatigue threshold.

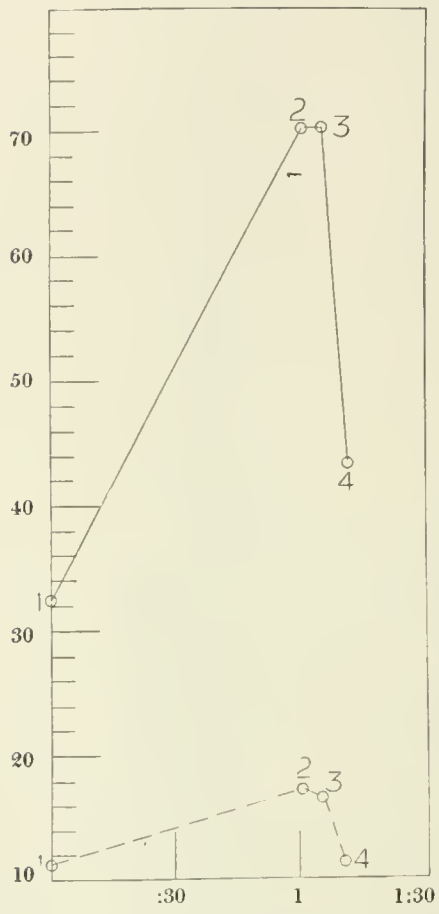


FIGURE 3. — A curve plotted from the data of one experiment. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate. The continuous line is the curve of the muscle, the broken line that of the nerve-muscle. The curve of the nerve-muscle is magnified ten times, that of the muscle is normal.

(1) Normal threshold stimulus. (2) The threshold after fatiguing the muscle for one hour. The muscle contracted 120 times per minute against a spring having an initial tension of 120 gm. (3) The threshold after five minutes' rest. (4) The threshold three minutes after the left splanchnic nerves were stimulated for 30 seconds.

That the action of adrenalin in reducing the fatigue threshold is not dependent upon an increase in blood pressure is evident, since the amount of adrenalin given has been shown by Cannon and Lyman [1] to produce a fall in arterial pressure.

To determine the effect of increased arterial pressure alone the adrenal glands (in some cases only the left)[2] were ligated and, after a period of fatigue of the

[1] CANNON and LYMAN: this Journal, 1912–13, xxxi, p. 376.

[2] According to Elliott, the innervation of the adrenal glands is homolateral. ELLIOTT: Journal of physiology, 1912, xliv, pp. 374–409.

muscle, the left splanchnic nerves were stimulated as in the experiment represented in Fig. 3. Four experiments were performed in which seven readings of the nerve-muscle and four of the muscle were taken. In these the average normal threshold of 1.4 β units for the nerve-muscle was increased by fatigue to 1.75 β units, an increase of 25 per cent. The threshold of the muscle was increased by fatigue from 24.6 to 43.1 β units, 75 per cent. The splanchnic nerves were then stimulated as described above. The average fatigue threshold in the nerve-muscle was decreased by this stimulation from 1.75 to 1.6 β units, a recovery of 42 per cent, and in the muscle from 43.1 to 34.5 β units, a recovery of 46 per cent. (See Table II, *B*.) The blood pressure in the majority of cases was increased more than 40 mm. of mercury. The original pressure in most cases was about 90 to 100 mm. of mercury as compared to 110 and 130 mm. in the animals in which the adrenal glands were intact. Evidently, therefore, increased blood pressure can in itself largely restore these fatigued structures to normal irritability.

The Fatigue Threshold of a Denervated Muscle as Affected by Adrenalin.

The results obtained on the denervated muscles were not quite as consistent as those on the normal muscle. In two experiments in which the left peroneus communis had been cut 6 and 7 days, adrenalin had no effect upon the fatigue threshold. Six later experiments were performed on animals in which the left peroneus communis nerve had been cut 7, 8, 12, 14, 15, and 16 days. In these, positive results were obtained and the recovery of the threshold by adrenalin was from 6 to 100 per cent. The average normal threshold for the six experiments, in which adrenalin was used to increase the fatigue irritability, was 47.8 β units. This was increased by fatigue to 138.8, an increase of 190 per cent. After an injection of adrenalin (0.1 to 0.5 cc.) this fatigue threshold was decreased to 102.9 β units, a recovery of 39 per cent.

Fig. 4 is a curve plotted from the data of one of the experiments performed to show the effect of small doses of adrenalin on the fatigue threshold of a denervated muscle. In this animal 2 cm. of the peroneus communis nerve were removed 7 days previous to

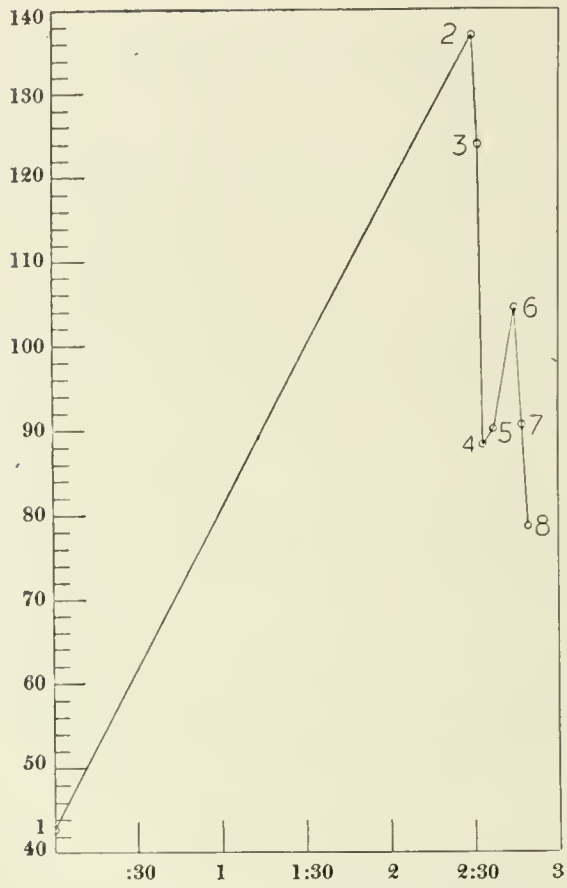


FIGURE 4. — A curve plotted from the data of one experiment performed on a denervated muscle. The peroneus communis nerve was cut seven days before this experiment was performed. The time interval in hours and minutes is represented on the abscissa; the value of the threshold in β units is represented on the ordinate.

(1) Normal threshold of muscle. (2) The threshold after the muscle was fatigued for two hours and thirty minutes. The muscle contracted 240 times a minute against a spring having an initial tension of 120 gm. (3) The threshold two minutes after an injection of adrenalin (0.5 cc. of a 1:100,000 solution). (4) Threshold taken one minute after (3). (5 and 6) Rests of four and eight minutes respectively. (7) Threshold two minutes after an injection of adrenalin (0.5 cc. of a 1:100,000 solution). (8) Threshold two minutes after (7).

the experiment. Similar results were obtained from animals in which the nerve was cut 9, 12, 14, 15, and 16 days. In all cases strong faradic stimulation of the distal end of the cut nerve gave no muscular response. In this figure (at 2) the threshold was taken after the muscle was fatigued for two hours and thirty minutes. The muscle contracted 240 times per minute against a spring having an initial tension of 120 gm. Through a cannula placed in the left external jugular vein 0.5 cc. of adrenalin was injected and two minutes later, with blood pressure slightly below the original level, the threshold reading (at 3) showed a recovery of 13 per cent, from 137.5 to 124.5 β units. One minute later, or three minutes after the injection, with blood pressure restored to the original level, the threshold (at 4) was decreased to 89.0 β units, a recovery of 51 per cent. After four more minutes the threshold (at 5) was 91.4 β units, and eight minutes later (at 6) 105 β units. At this point another 0.5 cc. adrenalin was injected intravenously, and after two minutes, with blood pressure restored, the threshold was reduced from 105 to 91.8 β units, a recovery of 48 per cent (at 7). Four minutes after the injection the threshold (at 8) dropped to 79.2 β units, a recovery of 61 per cent.

The lowering of the threshold stimulus in the denervated as well as in the fatigued normal muscle must be due to the action of adrenalin. In this case, however, the threshold did not remain lowered after the injection.

The question may arise as to whether or not the time allowed was sufficient for degeneration of the nerves. Howell and Huber found that seven days after the ulnar nerves of dogs were cut complete degeneration resulted and that partial irritability returned on the twenty-first day.[1] Huber found also that the nerve-endings in the interosseus muscle of the rabbit degenerated in from two to six days.[2] According to Bethe, seven to nine days are required in dogs and three to five days in rabbits for the nerve-endings to degenerate.[3] Tucket claims that the hypolemmal fibres of the flexor profundis muscle of the pigeon degenerate in two days or less.[4] Although there is considerable variation in the time required for degeneration of nerves in different animals and even in the different nerves of the same animal, it seems quite improbable that the peroneus communis nerve in the cat would require a longer time than the ulnar in the dog. Moreover, a marked similarity was found in the threshold stimuli of the denervated and curarized muscles. The average threshold stimulus for the 14 denervated animals was found to be 62.5 β units, and that for 14 curarized animals, in which there was complete immobility, was 63.5 β units. From these results there is little doubt that the nerve-endings of the denervated muscle were functionless. The nerves, moreover, were always tested with a strong faradic current before each experiment and were invariably found inactive.

Does Adrenalin Act by Bettering the Circulation?

The suggestion that adrenalin does not produce its beneficial effects on a fatigued muscle by bettering the circulation is made

[1] Howell and Huber: Journal of physiology, 1892, xiii, p. 358.

[2] Huber: this Journal, 1900, iii, p. 341.

[3] Bethe: Allgemeine Anatomie und Physiologie des Nervensystems, Leipzig, 1903, p. 162.

[4] Tucket: Reviewed by Langley in the Proceedings of the Royal Society of London, 1906, B, 78, p. 179.

by Cannon and Nice, who offer the following evidence[1]: "Against this supposition is the observation that when the arteries are deprived of their central innervation, as was the case with the arteries supplying the contracting muscle, adrenalin causes not a dilation but a constriction of the vessels.[2] And even if adrenalin did not cause vasoconstriction in this region, it could hardly produce much further dilation, for, as already noted, the vascular nerves had been cut and furthermore were being stimulated at a rate favorable to relaxation."

FIGURE 5. — Top record, blood pressure with mercury manometer. Middle record, contractions of the tibialis anticus muscle 240 times per minute against a spring with an initial tension of 120 gm. Bottom record (zero blood pressure) injection of 0.4 cc. of adrenalin (1:100,000). Time in half minutes.

Working upon this supposition, it was deemed advisable to make a comparative study of adrenalin and amylnitrite, since both may act as peripheral dilators.

Figs. 5 and 6 are curves obtained from the left tibialis anticus muscle. The rate of stimulation was 240 times a minute. The muscle in Fig. 5 contracted against a spring having an initial tension of 120 gm. and that in Fig. 6 having an initial tension of 100 gm. In Fig. 5 the muscle was after-loaded and in Fig. 6 it was loaded. The muscle lever magnified the contractions 4.4 times. In Fig. 5, at the point indicated on the base line, 0.4 cc. of adrenalin (1:100,000) was injected into the left external jugular vein. There resulted a fall of 25 mm. of mercury in the arterial

[1] CANNON and NICE: *Loc. cit.*, p. 55.

[2] CANNON and LYMAN: this Journal, 1913, xxxi, p. 376.

pressure and a concurrent betterment of 15 per cent in the height of contraction, requiring two minutes and fifteen seconds of fatigue before it returned to the former level. In Fig. 6, at the point indicated by an arrow, a solution of amylnitrite was injected into the right external jugular vein. There resulted a fall of 70 mm. of mercury in arterial pressure and a betterment of 4.1 per cent in the height of muscular contraction, requiring fifteen seconds of fatigue to decrease the height of contraction to its former level. In neither case did the blood pressure fall below the critical region.[1]

Although the fall in arterial pressure caused by dilation of the vessels due to amylnitrite was almost three times as great as that produced by the adrenalin, yet the resultant betterment was only about one-fourth the percentage height and lasted but one-ninth the time. The fact that the decrease in blood pressure caused by adrenalin cannot in itself account for the bettering effect upon the muscle curve has been shown by Cannon and Nice and myself.[2] In all cases in which these solutions caused an equal fall in arterial pressure, adren-

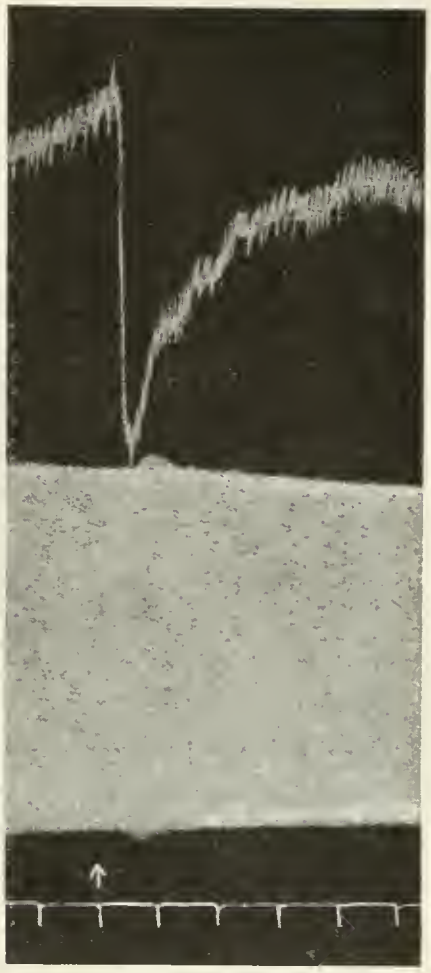


FIGURE 6.—Top record, blood pressure with mercury manometer. Middle record, contractions of tibialis anticus muscle 240 per minute against a spring with an initial tension of 100 gm. direct load. Bottom record (zero blood pressure) time in half minutes. The arrow indicates the point at which a solution of amylnitrite was injected.

[1] In some cases with amylnitrite the normal blood pressure, which was high, dropped sharply and fell below the critical region. GRUBER: this Journal, 1913, xxxii, p. 221. There resulted an increase in muscular contraction due to the betterment in circulation caused by the dilation of the vessels before the critical region was reached. During the time that the pressure was below the critical region the muscle contraction fell. As the blood pressure again rose to normal the muscle contraction increased similarly.

[2] CANNON and NICE: *Loc. cit.*, p. 55; GRUBER: *Loc. cit.*, p. 226.

alin caused a betterment in the height of contraction, while amyl-nitrite caused no appreciable change.

Still other results were obtained in which adrenalin caused no change in mean blood pressure but an increase in pulse pressure, with a resultant increase in the contraction. I found, as did Cannon and Nice, that the first increase in the arterial pressure during splanchnic stimulation is caused by the contraction of the

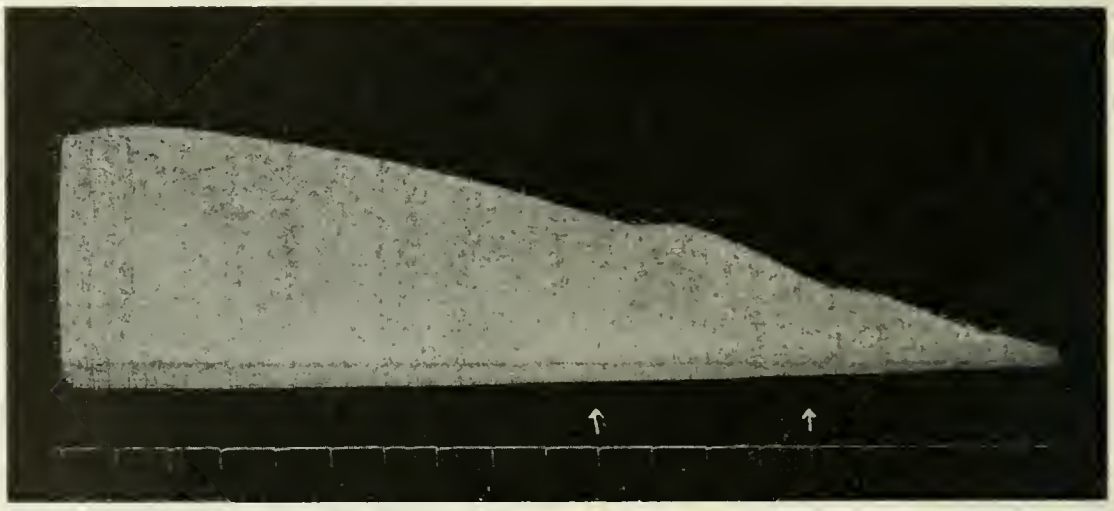


FIGURE 7. — Top record, contractions of tibialis anticus muscle 64 per minute against a spring having an initial tension of 120 gm. Bottom record, the time in half minutes. At the points indicated by arrows 0.5 cc. of adrenalin (1:1,000,000) was injected into the tube leading from the pressure bottle. The irrigation pressure was 95 mm. of mercury.

arteries in the splanchnic area.[1] This brings about a betterment in the height of muscular contraction, the period of which is very short.

It was found possible to prevent an increase of blood pressure during splanchnic stimulation by pulling on a fine cord looped about the aorta whenever the blood pressure showed a tendency to rise. Maintaining an even blood pressure did not, however, prevent a second proionged rise, which followed immediately upon the first in every case. The second rise must be due to the secretion of adrenalin during splanchnic stimulation.

Fig. 7 is offered as further evidence that adrenalin does not act by bettering the circulation or by liberation of sugar from the liver. Here the hind leg was irrigated as previously described (see

[1] CANNON and NICE: *Loc. cit.*, p. 48.

p. 337). In this record the left tibialis anticus muscle contracted 64 times a minute against a spring having an initial tension of 120 gms. The magnification of the contraction by the lever is 4.4 times. At the point indicated by the arrow 0.5 cc. of adrenalin (1:1,000,000) was injected into the running solution close to the cannula in the artery. There was a betterment of 2.8 per cent in the height of muscular contraction, which required thirty seconds of fatigue to restore it to the original slope of the curve. In every case the stream leading from the iliac vein ran more slowly after the injection, a fact which would indicate vasoconstriction of the vessels rather than vasodilation. Similar results were obtained when doses of 0.5 cc. of a 1:100,000 or of a 1:5,000,000 solution were injected. The strength of these solutions of adrenalin was much stronger than that produced in an animal by an injection of 0.1 cc. of a 1:100,000 solution into the jugular vein. In the latter case the dilution by the blood and tissue fluids would be approximately 1:200,000,000 when the adrenalin reached the fatigued muscle.

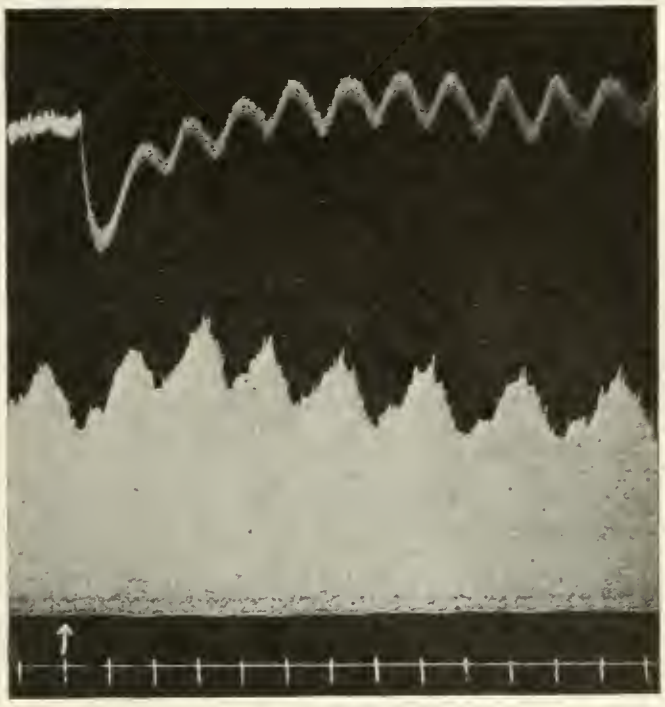


FIGURE 8. — Top record, blood pressure with mercury manometer. Middle record, contractions of a denervated muscle (tibialis anticus) 240 per minute against a spring having an initial tension of 120 gm. (peroneus communis nerve was cut nine days before this record was taken). Bottom record (zero blood pressure) time in half minutes. At the point indicated by an arrow 0.1 cc. of adrenalin (1:100,000) was injected intravenously.

IS THE ACTION OF ADRENALIN MUSCULAR OR NEURO-MUSCULAR?

Radwánska and Panella report that adrenalin acts either on the nerve trunk or on the neuro-muscular junction.[1] Oliver and

[1] RADWÁNSKA: *Loc. cit.*, pp. 728–736; PANELLA: Archives italiennes de biologie, 1907, xlvii, p. 30.

Schäfer and Dessy and Grandis report an effect on the muscle tissue itself.[1] That adrenalin lowers the fatigue threshold of a denervated muscle (7–16 days' degeneration) is cited in Fig. 4. Fig. 8 shows that it affects the height of muscular contraction. In this experiment the left tibialis anticus muscle was stimulated directly by thrusting platinum needle electrodes into it. The peroneus communis nerve supplying the muscle had been cut and 2 cm. removed nine days previous to the experiment. The rate of stimulation was 120 times per minute and the initial tension of the spring about 120 gms. The curve is magnified 4.4 times by the muscle lever. An injection of 0.1 cc. of adrenalin (1:100,000) was made into the left external jugular vein at the point indicated by an arrow. A fall in arterial pressure from 110 to 86 mm. of mercury and a simultaneous betterment of 20 per cent in the height of contraction were obtained. It required four minutes' fatigue to restore the muscle curve to its former level. Results similar to this were obtained from animals in which the nerve had been cut 7, 9, 12, 14, and 21 days. In all instances the nerve was inexcitable to strong faradic stimulation.

Discussion

From the above evidence one might infer that adrenalin acts primarily either on muscle substance or on the fatigue products. Dessy and Grandis concluded that adrenalin in some way neutralizes the fatigue products.[2] Albanese found in frogs and rabbits that, after the removal of the suprarenal capsules, these animals were prone to fatigue.[3] He therefore concluded that the function of the adrenal glands was to destroy or at least to transform the toxic substances, which as a result of muscular or nervous work are produced in the organism. Abelous and Langlois offered evidence that the suprarenal capsules in frogs and guinea pigs can modify, neutralize, or destroy poisons produced in the course of

[1] Oliver and Schäfer: *Loc. cit.*, p. 263; Dessy and Grandis: *Loc. cit.*, p. 231.

[2] Dessy and Grandis: *Loc. cit.*, p. 231.

[3] Albanese: Archives italiennes de biologie, 1892, xvii, p. 239.

muscular work, which accumulate in the organism after the destruction of the adrenal glands.[1]

Carrot and Josserand noted the influence of adrenalin on the blood pressure record before and after fatigue; 0.025 mg. of adrenalin per kilo injected in the femoral vein caused a rise of 10 cm. of mercury.[2] If injected into the femoral artery (leg at rest) the blood pressure was increased only 2 to 3 cm. of mercury. In the other femoral artery (leg tetanized for one-fourth hour) 0.055 mg. caused an elevation of only 1.5 cm. They claim that the adrenalin in the latter is neutralized by the fatigue products. Joteyko thinks that the chemical activity of adrenalin plays a role antagonistic to fatigue, and concludes, therefore, that it is a sarcoplasmic excitant.[3]

All these authors come to the conclusion that adrenalin produces its beneficial effects by neutralization, transformation, or destruction of the metabolites. It is quite true that all the phenomena shown in this paper can be explained on this assumption. It is contrary, however, to the conclusions of Radwánska, Panella, Cannon and Nice, and to results which I have obtained in experiments on the antagonism of adrenalin to curare which I shall soon publish.[4]

In Radwánska's experiments the muscle was stimulated with the nerve-endings intact. It seems, therefore, reasonable to suppose that in all cases he was stimulating nerve tissue. Since a muscle is more irritable when stimulated through its nerve than when stimulated directly (nerve and muscle), a slight change in the irritability of the muscle by adrenalin would naturally result in a greater contraction when the nerve was stimulated. The betterment in the results thus obtained, by stimulating the nerve directly, would be in proportion to the increase in irritability of the nerve over the muscle.[5]

[1] Abelous and Langlois: Archives de physiologie, 1892, xxiv, pp. 269–278. *Ibid.*, pp. 465–476.

[2] Carrot and Josserand: Comptes rendus, Société de Biologie, 1903, p. 51.

[3] Joteyko: Journal médical de Bruxelles, 1903, viii, p. 421.

[4] Radwánska: *Loc. cit.*, p. 728; Panella: *Loc. cit.*, p. 30; Cannon and Nice: *Loc. cit.*, p. 49.

[5] Gruber: this Journal, 1913, xxxii, p. 438. Figs. 1, 2, and 3 and Tables I and II of this article.

Panèlla's results can be interpreted to show that adrenalin is muscular in effect. Langley has demonstrated that nicotine and curare act upon a hypothetical "receptive substance." Since adrenalin has an action antagonistic to curare, adrenalin may be assumed also to act upon this substance.[1]

It is quite conclusive that adrenalin, in some way, causes a rapid recovery of the normal irritability of muscle after fatigue, and thus a betterment in the height of contraction. The question whether this is done by neutralizing, transforming, or destroying the fatigue toxins is still obscure. That the action may be on the muscle itself has been definitely shown in this paper; its effect, however, upon the nervous elements or on the region of the neuro-muscular union, cannot be denied.[2]

Summary

1. Adrenalin injected in small doses causes a recovery of the threshold irritability of the fatigued tibialis anticus muscle whether tested on the muscle or on the nerve-muscle.

2. Adrenalin acts quickly, requiring five minutes or less to produce its effect on the threshold. In that length of time, in some cases, it reduces the threshold to normal, whereas rest would require fifteen minutes to two hours.

3. Splanchnic stimulation causes, after fatigue, a quick recovery of the former threshold irritability. When the adrenal glands are tied off and the left splanchnic nerves stimulated there is also some recovery from the fatigue threshold of the nerve-muscle and of the muscle. This partial recovery is best accounted for as due to the increased blood pressure and improved circulation.

4. Adrenalin injected in small doses causes a recovery from the fatigue threshold of a denervated muscle (peroneus communis nerve cut six to sixteen days previous to the experiment).

[1] Langley: Proceedings of the Royal Society of London, 1906, lxxviii, B, p. 181. Journal of physiology, 1905–06, xxxiii, pp. 374–413.

[2] Oliver and Schäfer's betterment *Loc. cit.*, in muscular contraction may be accounted for in these ways: (1) storing up of adrenalin in the muscle, and (2) a small amount of fatigue before the muscles were excised, which was overcome in the muscle through which the adrenalin was allowed to pass.

5. Amylnitrite causes an increased height of muscular contraction simultaneously with a fall of blood pressure, due probably to vasodilation in the stimulated muscle and consequent betterment in circulation. This increase is small and of short duration. It occurs only when the fall in pressure is sharp and not below the critical region. If below this region there may be a brief betterment followed by a decrease in the height of contraction.

6. Adrenalin causes a betterment in contraction not wholly by vasodilation, as does amylnitrite, but specifically by action on the tissues or fatigue products. The betterment from adrenalin is prolonged and may occur even though no change in arterial pressure is brought about.

7. Adrenalin increases the height of contraction in an irrigated fatigued muscle when injected into the irrigating solution.

8. Adrenalin exerts an action on denervated muscle as well as on normal muscles. The percentage increase in the height of contraction here may be as great as in the normal muscles.

I wish to express my thanks to Dr. W. B. Cannon and to Dr. E. G. Martin for valuable suggestions offered me during these experiments.

THE EMERGENCY FUNCTION OF THE ADRENAL MEDULLA IN PAIN AND THE MAJOR EMOTIONS

By W. B. CANNON

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LIKE other endosecretory glands the adrenals have been studied by removing them and by injecting their extracts. Injection experiments have shown that the substance produced by the adrenal medulla (adrenin, adrenalin, epinephrin, etc.) is capable of producing many profound bodily changes. The most important of these changes are: a cessation of the activities of the alimentary canal; a notable shifting of the circulation from the great vessels of the abdomen to the lungs, heart, limbs and central nervous system; an increased cardiac vigor; and an augmentation of the sugar content of the blood. Little attention has been paid to the important question of the possible value of these striking bodily alterations as they might occur in the natural life of animals. It is significant that these effects are caused also by nervous discharges along sympathetic pathways — the discharges that are sent forth in crises of pain and great emotion. During the past three years, in a series of investigations conducted in this laboratory,[1] we have attempted to gain insight into the meaning of the changes wrought by adrenalin or increased adrenal secretion, and in this paper I propose to discuss the bearings of our results.

Adrenalin is Liberated Normally in Fear, Rage, Asphyxia and Pain

A point of prime importance in the functioning of the adrenal medulla is its subjection to central nervous influences coming to it by way of the splanchnics. With a variety of methods, in the

[1] CANNON and DE LA PAZ: this Journal, 1911, xxviii, p. 64. CANNON and HOSKINS: *ibid.*, 1911, xxix, p. 274. CANNON, SHOHL and WRIGHT: *ibid.*, 1911, xxix, p. 280. CANNON and LYMAN: *ibid.*, 1913, xxxi, p. 376. CANNON and NICE: *ibid.*, 1913, xxxii, p. 44. GRUBER: *ibid.*, 1913, xxxii, pp. 221, 438; and 1914, xxxiii, p. 335.

hands of various investigators,[1] proof has been brought that artificial stimulation of the splanchnic nerves will induce secretory activity in the adrenal medulla, and that in consequence adrenalin is increased in the blood. Thus the fact is now securely established that there exists in the body a mechanism by which this endosecretory gland can be made to discharge its products promptly into the circulation.

The question whether the medulla is stimulated to activity by nervous impulses aroused by the natural events in the course of an animal's life was taken up by de la Paz and me about three years ago.[2] We found that when a cat was frightened by a barking dog the blood in the cat's vena cava close in front of the opening of the adrenal veins gave definite evidence of the presence of adrenalin (relaxation of the rhythmically contracting intestinal strip), whereas blood from the same region previous to the excitement was ineffective. Later Hoskins and I found that strong stimulation of the sciatic nerve in an anaesthetized animal—such stimulation as would cause severe pain if the animal were not anaesthetized— and also asphyxia, resulted in greater activity of the adrenal medulla, as indicated by the increased amount of adrenalin in the cava blood.[3]

Our observation on asphyxia has been supported by Borberg and Fridericia,[4] and also by Starkenstein,[5] who found that an increase of CO_2 in the blood lessens the chromaffine substance in the adrenal medulla. And recently Czubalski also has inferred, from the rise of blood-pressure in asphyxia when the adrenals are intact and the absence of the rise if the adrenals are removed, that asphyxia sets free adrenalin in the blood.[6]

[1] *See* Dreyer: this Journal, 1898–99, ii, p. 219. Tscheboksaroff: Archiv für die gesammte Physiologie, 1910, cxxxvii, p. 103. Asher: Zentralblatt für Physiologie, 1910, xxiv, p. 927. Kahn: Archiv für die gesammte Physiologie, 1911, cxl, p. 240. Meltzer and Joseph: this Journal, 1912, xxix, p. xxxiv. Elliott: Journal of physiology, 1912, xliv, p. 400. Cannon and Lyman: *Loc. cit.*, p. 377; and others.

[2] Cannon and de la Paz: *Loc. cit.*, p. 67.

[3] Cannon and Hoskins: *Loc. cit.*, p. 278.

[4] Borberg: Skandinavisches Archiv für Physiologie, 1913, xxviii, p. 125.

[5] Starkenstein: Zeitschrift für experimentelle Pathologie und Therapie, 1911, x, p. 95.

[6] Czubalski: Zentralblatt für Physiologie, 1913, xxvii, p.580.

Our observations on fear and pain have been supported by Elliott's study of the adrenalin content of the glands as affected by experimental procedures. He found that "fright," induced in cats by morphia or by β-tetrahydronaphthylamine, exhausts the glands, and that excitation of afferent nerves, such as the great sciatic, also causes adrenalin to disappear.[1] These results are what could be reasonably expected, for major emotions, as fear and rage, and such sensory stimulation as in a conscious animal would be painful are known to be accompanied by nerve impulses passing out via sympathetic fibres — impulses causing dilatation of the pupils, inhibition of gastric katastalsis and secretion, and contraction of arterioles.[2] And, as previously stated, the adrenal medulla has been proved to manifest increased secretory activity when affected by nerve impulses coming via these same pathways.

Blood Sugar is Increased in Fear, Rage, Asphyxia and Pain if the Adrenals are Intact

Artificial stimulation of splanchnic nerves not only liberates adrenalin but also releases sugar from the liver.[3] If, however, the adrenals are removed from the body, splanchnic stimulation will not evoke glycosuria.[4] The participation of the adrenal medulla, therefore, seems to be essential for the mobilization of sugar in the blood, when that is accomplished by nerve impulses.

As pointed out above, adrenal secretion is increased in major emotional states, in asphyxia, and on stimulation of nerves for pain; hyperglycaemia is the normal accompaniment of such experimental nervous stimulations as evoke an increased adrenal secretion; therefore, that fear and rage, pain and asphyxia would give rise to hyperglycaemia might reasonably be expected.

[1] Elliott: *Loc. cit.*, p. 409.

[2] *See* Cannon: The Mechanical Factors of Digestion, London and New York, 1911, p. 217; also American journal of the medical sciences, 1909, cxxxvii, p. 480.

[3] *See* Macleod: Diabetes: its Pathological Physiology, London, 1913, pp. 61–62.

[4] *See* Gautrelet and Thomas: Comptes rendus de la Société de Biologie, 1909, lxvii, p. 233. Macleod: Proceedings of the Society for Experimental Biology and Medicine, 1911, viii, p. 110.

The influence of asphyxia as a highly potent condition for the mobilization of sugar in the blood is well established.[1] Starkenstein has shown, however, that asphyxia due to carbon monoxide poisoning is not accompanied by hyperglycaemia if the adrenal glands have been removed.[2]

That experimental procedures attended by pain result in the appearance of sugar in the urine was demonstrated many years ago by Böhm and Hoffman.[3] Their observations on cats have proved true also of rabbits;[4] and recently it has been shown that an operation involving some pain increases blood sugar in dogs.[5]

That pure emotional excitement — fear or rage — will have the same effect was proved when Shohl, Wright and I obtained glycosuria in cats by fastening them to a comfortable holder or by placing them in small cages and permitting a dog to bark at them. Whether glycosuria appeared promptly or not depended on the animal's emotional reaction to its experience. Neither pain, cooling nor being bound, therefore, was a factor in the result — the essential element was the fright or rage of the animal.[6] Our conclusion has been confirmed by one of my former students, Dr. W. G. Smillie, who found that 4 of 9 medical students (all normally aglycosuric) had glycosuria after a hard examination, and only 1 of the 9 had glycosuria after an easier examination.[7] Also Rolly and Opper-

[1] For evidence and for reference to literature, *see* Bang: Der Blutzucker, Wiesbaden, 1913, pp. 104–108.

[2] Starkenstein: *Loc. cit.*, p. 94. He was able to produce glycosuria in the absence of the adrenals by strong stimulation of the central end of the cut vagus; he therefore concluded that the sympathetic impulses are primary and that the adrenals are accessory in evoking glycogenolysis.

[3] Böhm and Hoffman: Archiv für experimentelle Pathologie und Pharmakologie, 1878, viii, p. 295.

[4] Eckhard: Zeitschrift für Biologie, 1903, xliv, p. 408.

[5] Loewy and Rosenberg: Biochemische Zeitschrift, 1913, lvi, p. 114.

[6] Cannon, Shohl and Wright: *Loc. cit.*, p. 283.

[7] The tests, which were positive with Fehling's solution, Nylander's reagent, and also with phenyl-hydrazine, were made on the first urine passed after the examination. Mr. C. H. Fiske and I have found sugar in the urine in 12 of 25 members of the Harvard University foot-ball squad, immediately after the final and most exciting contest of the season. Five of the positive cases were substitutes who were not called upon to enter the game. The only spectator whose urine was examined had a marked glycosuria.

mann, Jacobsen, and Hirsch and Reinbach have recently reported that the mere handling of a rabbit preparatory to operating on it will increase the blood sugar (in some cases from .10 to .23 and .27 per cent) and may result in glycosuria.[1] Indeed, the readiness with which this response occurs has been pointed out as a source of error in estimates of the "normal" sugar content of the blood.

In our studies[2] we observed that animals which had glycosuria when bound for about an hour, failed to have it after careful adrenalectomy, although bound between two and three times as long as before, and although still manifesting the same degree of excitement which they had manifested previous to the operation. This result harmonizes with that already reported that the presence of the adrenals is necessary when hyperglycaemia is to be produced by splanchnic stimulation.

Fear, rage, asphyxia and pain, therefore, are accompanied by an increased discharge of adrenalin into the blood, and by a freeing of stored glycogen from the liver for circulation through the body as glucose. The hyperglycaemia and the adrenalinaemia are both due to nervous discharges. Since, in the absence of the adrenals, nerve impulses fail to evoke sugar; and since, in the absence of nerve impulses, a sufficient injection of adrenalin will evoke sugar, the inference seems justified that, for the ready increase of blood sugar by nervous discharges in emotions, circulating adrenalin must be simultaneously increased. What explanation can be offered for this remarkable outpouring from the adrenal medulla and the concomitant glycogenolysis that floods the body with sugar?

The Reflex Nature of Bodily Responses to Pain and the Major Emotions

The most significant feature of these bodily reactions to pain and to emotion-provoking objects is that they are of the nature of reflexes, — they are not willed movements, indeed they are often distressingly beyond the control of the will. The pattern of the

[1] Rolly and Oppermann: Biochemische Zeitschrift, 1913, xlix, p. 201. Jacobsen: *ibid.*, 1913, li, p. 449. Hirsch and Reinbach: Zeitschrift für physiologische Chemie, 1913, lxxxvii, p. 122.

[2] Cannon, Shohl and Wright: *Loc. cit.*, p. 285.

reaction, in these as in other reflexes, is deeply inwrought in the workings of the nervous system, and when the appropriate occasion arises, typical organic responses are evoked through inherent automatisms.

It has long been recognized that the most characteristic feature of reflexes is their "purposive" nature, or their utility either in preserving the welfare of the organism or in safeguarding it against injury. The reflexes of sucking, swallowing, vomiting and coughing, for instance, need only to be mentioned to indicate the variety of ways in which reflexes favor the continuance of existence. When, therefore, these automatic responses accompanying pain and fear and rage — the increased discharge of adrenalin and sugar — are under consideration, it is reasonable to enquire first as to their utility.

Numerous ingenious suggestions have been offered to account for the more obvious changes accompanying emotional states — as, for example, the bristling of the hair and the uncovering of the teeth in an access of rage.[1] The most widely applicable explanation proposed for these spontaneous reactions is that during the long course of racial experience they have been developed for quick service in the struggle for existence. McDougall has suggested that an association has become established between peculiar emotions and these ingrained native reactions; thus the emotion of fear is associated with the instinct for flight, and the emotion of anger or rage with the instinct for fighting or attack.[2] Crile likewise has emphasized the importance of adaptation and natural selection, operative through age-long racial experience, in enabling us to account for the already channelled responses which we find established in our nervous organization. And on a principle of "phylogenetic association" he assumes that fear, born of innumerable injuries in the course of evolution, has developed into portentous foreshadowing of possible injury and has become, therefore, capable of arousing in the body all the offensive and defensive activities that favor the survival of the organism.[3]

[1] *See* Darwin: Expression of Emotions in Man and Animals, New York, 1905, pp. 101, 117.

[2] McDougall: Introduction to Social Psychology, London, 1908, pp. 49, 59.

[3] Crile: Boston medical and surgical journal, 1910, clxiii, p. 893.

Because the adrenalinaemia and the hyperglycaemia following painful or strong emotional experiences are reflex in character, and because reflexes as a rule are useful responses, we are justified in the assumption that under these circumstances the increase of adrenalin and sugar in the blood is useful. What then is the possible value of these reactions?

The Utility of Sugar and Adrenalin Liberated in Pain and the Major Emotions

That the outpouring of adrenalin and sugar in conditions of pain and the major emotions has value for the organism was the leading idea in the researches recently reported from this laboratory.[1] In order that these reactions may be useful they must be *prompt*. Such is the case. Some unpublished observations made in this laboratory show that the latent period of adrenal secretion, when the splanchnic nerve is stimulated below the diaphragm, is not longer than 16 seconds; and Macleod states that within a few minutes after splanchnic stimulation the sugar in the blood rises between 10 and 30 per cent.[2] The two secretions are, therefore, almost instantly ready for service.

Conceivably the two secretions might act in conjunction or each might have its own function alone. Thus adrenalin might serve in co-operation with nervous excitement to produce hyperglycaemia, or it might have that function and other functions quite apart from that. Before these possibilities are considered, however, the value of the hyperglycaemia itself will be discussed.

The Utility of Increased Blood Sugar. — In the paper on emotional glycosuria previously mentioned,[3] a clue was taken from McDougall's suggestion of a relation between "flight instinct" and "fear emotion," and "pugnacity instinct" and "anger emotion." And the point was made that, since the fear emotion and the anger emotion are, in wild life, likely to be followed by activities (running or fighting) which require contraction of great muscular masses in supreme and prolonged struggle, a mobilization of sugar

[1] *See* Cannon: Proceedings American Philosophical Society, 1911, l, p. 227.

[2] Macleod: Diabetes, etc., p. 80.

[3] Cannon, Shohl and Wright: *Loc. cit.*, p. 286.

in the blood might be of signal service to the laboring muscles. Pain — and fighting is almost certain to involve pain — would, if possible, call forth even greater muscular effort. "In the agony of pain almost every muscle of the body is brought into strong action," Darwin wrote, for "great pain urges all animals, and has urged them during endless generations, to make the most violent and diversified efforts to escape from the cause of suffering." [1]

That muscular work is performed by energy supplied in carbonaceous material is shown by the great increase of carbon-dioxide output in severe muscular work, which may exceed twenty times the output during rest. Furthermore, the storage of glycogen in muscle, and the disappearance of this glycogen deposit from excised muscle stimulated to activity,[2] or its reduction after excessive contractions produced by strychnine,[3] and the lessened ability of muscles to work if their glycogen store has been reduced,[4] and the simple chemical relation between sugar and the lactic acid which appears when muscles are repeatedly made to contract, are all indications that carbohydrate (sugar and glycogen) is the elective source of energy for contraction. This conclusion is supported in recent careful studies by Benedict and Cathcart, who have shown that a small but distinct increase in the respiratory quotient occurs during muscular work, and that a decrease in the quotient follows, thus pointing to a larger proportion of carbohydrate burned during muscular work than before or after — i.e., a call on the carbohydrate deposits of the body.[5]

[1] Darwin: *Loc. cit.*, p. 72. It is recognized that both pain and the major emotions may have at times depressive rather than stimulating effects. Though severe pain may soon induce extreme prostration, the whip and spur illustrate its primary exciting action. And though fear may become the most depressing of all emotions, it acts at first as a powerful stimulus. "A man or animal driven through terror to desperation is endowed with wonderful strength, and is notoriously dangerous in the highest degree." (Darwin: *Loc. cit.*, p. 81.)

[2] Nasse: Archiv für die gesammte Physiologie, 1869, ii, p. 106; 1877, xiv, p. 483.

[3] Frentzel: Archiv für die gesammte Physiologie, 1894, lvi, p. 280.

[4] Zuntz: Oppenheimer's Handbuch der Biochemie, Jena, 1911, iv (first half), p. 841.

[5] Benedict and Cathcart: Muscular Work, a metabolic study, Washington, 1913, pp. 85–87.

Whether circulating sugar can be immediately utilized by active muscles has been a subject of dispute. The claim of Chauveau and Kaufmann that a muscle uses about three and a half times as much blood sugar when active as when resting,[1] although supported by Quinquaud,[2] and by Morat and Dufourt,[3] has been denied by Pavy, who failed to find any difference between the sugar content of arterial and venous blood when the muscle was contracting;[4] and also by Magnus-Levy, who has estimated that the amount of change in sugar content of the blood passing through a muscle must be so slight as to be within the limits of the error of analysis.[5] On the other hand, when blood or Ringer's solution is repeatedly perfused through contracting heart muscle, the evidence is clear that the contained sugar may more or less completely disappear. Thus Locke and Rosenheim found that from 5 to 10 centigrams of dextrose disappeared from Ringer's solution repeatedly circulated through the rabbit heart for eight or nine hours.[6] And recently Patterson and Starling have shown that if blood is perfused repeatedly through a heart-lung preparation for three or four hours, and the heart is continually stimulated by adrenalin added to the blood, the sugar in the blood wholly vanishes; or if the supply of sugar is maintained, the consumption may rise as high as 8 mgms. per gram per hour — about four times the usual consumption.[7] When an animal is eviscerated it may be regarded as a preparation in which the muscles are perfused with their proper blood, pumped by the heart and oxygenated by the lungs. Under these circumstances, the percentage of sugar in the blood steadily falls,[8] because the utilization by the tissues is not

[1] Chauveau and Kaufmann: Comptes rendus, Académie des Sciences, 1886, ciii, p. 1062.

[2] Quinquaud: Comptes rendus, Société de Biologie, 1886, xxxviii, p. 410.

[3] Morat and Dufourt: Archives de physiologie, 1892, xxiv, p. 327.

[4] Pavy: The Physiology of the Carbohydrates, London, 1894, p. 166.

[5] Magnus-Levy: v. Noorden's Handbuch der Pathologie des Stoffwechsels, 1906, i, p. 385.

[6] Locke and Rosenheim: Journal of physiology, 1907, xxxvi, p. 211.

[7] Patterson and Starling: Journal of physiology, 1913, xlvii, p. 143.

[8] *See* Macleod and Pearce: this Journal, 1913, xxxii, p. 192. Pavy and Siau: Journal of physiology, 1903, xxix, p. 375. Macleod: this Journal, 1909, xxiii, p. 278.

compensated for by further supply from the liver. Thus, although there may be doubt that analyses of sugar in the blood flowing into and out from an active muscle during a brief period can be accurate enough to prove a clear difference, the evidence from the experiments above cited shows that when the supply of sugar is limited it disappears to a greater or less degree when passed repeatedly through muscular organs.

The argument may be advanced, of course, that the sugar which thus disappears is not directly utilized, but must first be changed to glycogen. There is little basis for this assumption. There is, however, considerable evidence that increasing blood sugar does, in fact, directly increase muscular efficiency. Thus Locke proved that if oxygenated salt solution is perfused through the rabbit heart, the beats begin to weaken after one or two hours; but if now 0.1 per cent dextrose is added to the perfusing fluid the beats at once become markedly stronger and may continue with very slow lessening of strength as long as seven hours.[1] And Schumberg noted that when he performed a large amount of general bodily work (thus using up blood sugar) and then tested flexion of the middle finger in an ergograph, the ability of the muscle was greater if he drank a sugar solution than if he drank an equally sweet solution of "dulcin." He did not know during the experiment which solution he was drinking.[2] These observations have been confirmed by Prantner and Stowasser, and by Frentzel.[3] In experiments on cats Lee and Harrold found that when sugar is removed from the animal by means of phlorhizin the tibialis anticus is quickly fatigued; but if, after the phlorhizin treatment, the animal is given an abundance of sugar and then submitted to the test, the muscle shows a much larger capacity for work.[4] All this evidence is, of course, favorable to the view that circulating sugar may be quickly utilized by contracting muscles.

From experimental results presented above it is clear that muscles work preferably by utilizing the energy stored in sugar, that great muscular labor is capable of considerably reducing the

[1] Locke: Centralblatt für Physiologie, 1900, xiv, p. 671.

[2] Schumberg: Archiv für Physiologie, 1896, p. 537.

[3] Frentzel: Archiv für Physiologie, 1899, Supplement Band, p. 145.

[4] Lee and Harrold: this Journal, 1900, iv, p. ix.

quantity of stored glycogen and of circulating sugar, and that under circumstances of a lessened sugar content the increase of blood sugar considerably augments the ability of muscles to continue contracting. The conclusion seems justified, therefore, that the hyperglycaemia attendant on the major emotions and pain would be of direct benefit to the organism in the strenuous muscular efforts involved in flight or conflict or struggle to be free.

The Utility of Increased Adrenalin in the Blood. — In early work on the effects of removal of the adrenal bodies, muscular weakness was not infrequently noted. In 1892 Albanese showed that muscles stimulated after adrenalectomy were much more exhausted than when stimulated the same length of time in the same animal before the removal.[1] Similarly Boinet reported that rats recently deprived of their adrenal glands were much more quickly exhausted in a revolving cage than were normal animals.[2] A beneficial effect of adrenal extract on fatigued muscle, even when applied to the solution in which the isolated muscle is contracting, was claimed by Dessy and Grandis, who studied the phenomenon in the salamander.[3]

It seemed possible, because of the early evidence that adrenalectomy has a debilitating effect on muscular power, and that injection of adrenal extract has an invigorating effect, that increased adrenal secretion, as a reflex result of pain or the major emotions, might not only be useful in helping to mobilize sugar, but also might act in itself as a dynamogenic factor in the performance of muscular work. On the basis of this possibility Nice and I tested the effect of stimulating the left splanchnic nerve (thus causing adrenal secretion), or injecting adrenalin, on the contraction of the fatigued tibialis anticus.[4] We found that when

[1] Albanese: Archives italiennes de biologie, 1892, xvii, p. 243.

[2] Boinet: Comptes rendus, Société de Biologie, 1895, xlvii, pp. 273, 498.

[3] Dessy and Grandis: Archives italiennes de biologie, 1904, xli, p. 231. Biedl's observation (*See* Biedl: Innere Sekretion, Second Edition, Leipzig, 1913, i, p. 376), that in selachians removal of the interrenal bodies (corresponding to the adrenal cortex) results in muscular weakness, might indicate that the cortex was directly involved in muscular efficiency, but the failure of the animals to take food after undergoing the operation renders that conclusion hazardous.

[4] Cannon and Nice: *Loc. cit.*, p. 54.

arterial pressure was of normal height, and was prevented from rising in the legs while the splanchnic was being stimulated, there was a distinct rise in the height of contraction of the fatigued muscle. We drew the inference that adrenalin set free in the blood may operate favorably to the organism by preparing fatigued muscles for better response to the nervous discharges sent forth in great excitement.

This inference has been further tested during the past summer by one of my students, Mr. C. M. Gruber, who has examined the effects of minute amounts of adrenalin (0.1 or 0.5 cc. of 1:100,000), and also of splanchnic stimulation, on the threshold stimulus of fatigued neuromuscular and muscular apparatus. Fatigue raises the threshold not uncommonly 100 or 200 per cent and in some instances as much as 600 per cent. Rest will restore the normal threshold in periods varying from 15 to 120 minutes, according to the length of previous stimulation. If a small dose of adrenalin is given, however, the normal threshold may be restored in 3 to 5 minutes.[1]

From the foregoing evidence the conclusion is warranted that adrenalin, when freely liberated in the blood, not only aids in bringing out sugar from the liver's store of glycogen, but also has a remarkable influence in quickly restoring to fatigued muscles, which have lost their original irritability, the same readiness for response which they had when fresh. Thus the adrenalin set free in pain and in fear and rage would put the muscles of the body unqualifiedly at the disposal of the nervous system; the difficulty which nerve impulses might have in calling the muscles into full activity would be practically abolished; and this provision, along with the abundance of energy-supplying sugar newly flushed into the blood, would give to the animal in which these mechanisms are most efficient the best possible conditions for putting forth supreme muscular efforts.[2]

Does Adrenalin Normally Secreted Inhibit the Use of Sugar

[1] *See* GRUBER: this Journal, 1914, xxxiii, p. 354.

[2] If these results of emotion and pain are not "worked off" by action, it is conceivable that the excessive adrenalin and sugar in the blood may have pathological effects (*Cf.* CANNON: Journal of the American Medical Association, 1911, lvi, p. 742).

by the Tissue? — The only evidence opposed to the conclusion which has just been drawn is that which may be found in results recently reported by Wilenko. He injected adrenalin into urethanized rabbits, usually 1 mgm. per kilo body weight, and then found that the animals did not oxidize any part of an intravenous injection of glucose. Rabbits supplied with glucose in a similar manner, but not given adrenalin, have an increased respiratory quotient. Wilenko concluded therefore that adrenalin lessens the capacity of the organism to burn carbohydrates.[1] In a later paper he reported that adrenalin when added to Locke's solution (with glucose), and perfused through the isolated rabbit heart, notably increases the use of sugar by the heart (from 2.2–2.8 to 2.9–4.3 mgm. glucose per gm. heart muscle per hour), but that the heart removed after the animal had received a subcutaneous injection of adrenalin uses much less sugar, only 0.5–1.2 mgm. per gm. per hour. From these results Wilenko concludes that adrenalin glycosuria is the result of the disturbance of the *use* of sugar — an effect which is not direct on the sugar-consuming organ, but indirect through action on some other organ.[2]

Wilenko's conclusion fails to account readily for the disappearance of glycogen from the liver in adrenalin glycosuria. Furthermore, Lusk has recently reported that the subcutaneous administration of adrenalin (1 mgm. per kilo body weight) to dogs, simultaneously with 50 grams of glucose by mouth, interferes not at all with the use of the sugar — the respiratory quotient remains for several hours at 1.0; i.e., at the figure which glucose alone would have given.[3] In other words Lusk's results with dogs are directly contradictory to Wilenko's results with rabbits. Nevertheless, Wilenko's conclusion might be quite true for the glycosuria produced by adrenalin alone (which must be excessive), and yet have no bearing whatever on the glycosuria produced physiologically by splanchnic stimulation, even though some adrenalin is thereby simultaneously liberated.

[1] Wilenko: Biochemische Zeitschrift, 1912, xlii, p. 58.

[2] Wilenko: Archiv für experimentelle Pathologie und Pharmakologie, 1913, lxxi, p. 266.

[3] Lusk: Proceedings of the Society for Experimental Biology and Medicine, 1914, xi, p. 49.

The amount of adrenalin injected to produce adrenalin glycosuria is enormous. Mr. H. Osgood has studied in this laboratory the effects on blood pressure of alternately stimulating the left splanchnic nerve (with the splanchnic vascular area eliminated) and injecting adrenalin, and by this method[1] has shown that the amount secreted after five seconds of stimulation varies between 0.0015 and 0.007 mgm. If 0.005 mgm. is taken as rather high average figure, and doubled (for the two glands), the amount would be 0.01 mgm. To produce adrenalin glycosuria an animal weighing 2 kilos would be injected with two hundred times this amount. It is granted that more adrenalin would be secreted if the nerves were stimulated longer than five seconds, and that with subcutaneous or intraperitoneal injection (to produce glycosuria), the amount of adrenalin in the blood at one time would not be so great as if the injection were intravenous; but even with these concessions the amount of adrenalin in the blood needed to produce glycosuria is probably much above the amount following physiological stimulation of the glands.

Other evidence that the amount of adrenalin discharged when the glands are stimulated is not so great as the amount needed to produce glycosuria when acting alone is presented in experiments by Macleod. He found that if the nerve fibres to the liver were destroyed, stimulation of the splanchnic, which would cause increased adrenal secretion, did not increase the blood sugar. The hyperglycaemia due to splanchnic stimulation, therefore, is a nervous effect, dependent, to be sure, on the presence of adrenalin in the blood, but the amount of adrenalin present is not in itself capable of evoking the hyperglycaemia.[2]

Furthermore, the hyperglycaemia following splanchnic stimulation may long outlast the stimulation period. The adrenals, however, as has been demonstrated by Osgood in this laboratory, are soon fatigued, and fail to respond to repeated stimulation. They seem to be incapable of prolonged action.

Again, as Macleod has shown, hyperglycaemia can be induced, if the adrenals are intact, merely by stimulating the nerves going to the liver.[3] The hyperglycaemia of splanchnic origin, therefore,

[1] *See* Elliott: Journal of physiology, 1912, xliv, p. 376.

[2] Macleod: Diabetes, etc., pp. 64–73. [3] Macleod: Diabetes, etc., pp. 68–72.

is not due to a disturbance of the *use* of sugar in the body, as Wilenko claims for the hyperglycaemia after adrenalin injection, but is a result of a hyperglycogenolysis of nervous origin.

We may conclude therefore that since the conditions of Wilenko's observations are not comparable with emotional conditions, his inferences are not pertinent to the present discussion; that when both adrenalin and sugar are increased in the blood as a result of excitement, the hyperglycaemia is not due to adrenalin inhibiting the use of sugar by the tissues, and that there is no evidence at present to show that the brief augmentation of adrenal discharge, following excitement or splanchnic stimulation, affects in any deleterious manner the utilization of sugar as a source of energy. Indeed, the observation of Wilenko and of Patterson and Starling, above mentioned, that adrenalin increases the use of sugar by the heart, may signify that a physiological discharge of the adrenals can have a favorable rather than an unfavorable effect on the employment of sugar by the tissues.

The Vascular Changes Produced by Adrenalin are Favorable to Great Muscular Exertion

Quite in harmony with the foregoing argument that sugar and adrenalin, which are poured into the blood during emotional excitement, render the organism more efficient in the physical struggle for existence, are the vascular changes wrought by increased adrenalin, probably in co-operation with sympathetic innervations. Through oncometric studies, Oliver and Schäfer proved that the viscera of the splanchnic area — as the spleen, the kidneys and the intestines — suffer a considerable diminution of volume when adrenalin is administered, whereas the limbs into which the blood is forced from the splanchnic region actually increase in size.[1] In other words, at times of stress blood may be driven out of vegetative organs of the interior, which serve the routine needs of the body, into the skeletal muscles, which have to meet by extra action the urgent demands of conflict.

But there are exceptions to the statement that by adrenalin the viscera are emptied of their blood. It is well known that adrenalin

[1] Oliver and Schäfer: Journal of physiology, 1895, xviii, p. 240.

has a vasodilator, not a vasoconstrictor, effect on the arteries of the heart; it is well known also that adrenalin affects the intracranial and the pulmonary vessels only slightly, if at all.[1]

Thus the absolutely essential organs — the "tripod of life" — the heart, lungs and brain (as well as the skeletal muscles) — are, in times of excitement, when the adrenal glands discharge, abundantly supplied with blood taken from organs of less importance in critical moments.

The Muscles May Help Themselves by Operating the Adrenal Mechanism

As previously stated, Hoskins and I have shown that asphyxia causes an augmented secretion of adrenalin.[2] Asphyxia is a long recognized method of inducing hyperglycaemia. Hoskins and McClure, in extension of the theory which has underlain the researches summarized in this paper, have suggested that excessive muscular activity, such as might attend flight or conflict, would lead to partial asphyxia, and that this condition would naturally act in conjunction with emotional excitement and pain to bring forth a still greater adrenal discharge and a still greater output of sugar from the liver. And these in turn would serve the laboring muscles in the manner already described.[3] This suggestion is in accord with Macleod's that the increased glycogenolysis produced by muscular exercise is possibly associated with increased carbon dioxide in the blood.[4] And it also harmonizes with Zuntz's statement that the asphyxia of great physical exertion may call out sugar to such a degree that, in spite of the increased use of it in the active muscles, glycosuria may ensue.[5]

Conclusion

To what extent the slight constant secretion of the adrenal glands serves the organism is not yet well determined. As several observers have shown, the first effect of injecting small amounts

[1] *See* Biedl: *Loc. cit.*, pp. 434, 435.
[2] Cannon and Hoskins: *Loc. cit.*, p. 275.
[3] Hoskins and McClure: Archives of internal medicine, 1912, x, p. 355.
[4] Macleod: Diabetes, etc., p. 184. [5] Zuntz: *Loc. cit.*, p. 854.

of adrenalin into carnivorous animals is to lower blood pressure.[1] Adrenal secretion cannot be, therefore, at least among the carnivora, a direct factor in maintaining the normal high tonus of the vasomotor system. It is probable, however, that incredibly minute amounts of this substance in the circulating blood somehow sensitize the myoneural junctions of the sympathetic system, and thus aid the nervous action.[2] Such quiet service, however, is quite distinct from the profound changes in the organism which larger amounts of adrenalin are capable of provoking or helping to provoke.

The cessation of activities of the alimentary canal (thus freeing energy for other parts); the shifting of the blood from the less insistent abdominal viscera to the organs immediately essential to life itself, such as the lungs, the heart, the central nervous system and, at critical moments, the skeletal muscles as well; the increased cardiac vigor; the quick abolition of the effects of muscular fatigue, the mobilizing of energy-giving sugar in the circulation — these are the changes which occur when fear or rage or pain causes the adrenal glands to pour forth an excessive secretion. These changes in the body are, each one of them, *directly serviceable in making the organism more efficient in the struggle which fear or rage or pain may involve;* for fear and rage are organic preparations for action, and pain is the most powerful known stimulus to supreme exertion. The organism which with the aid of increased adrenal secretion can best muster its energies, can best call forth sugar to supply the laboring muscles, can best lessen fatigue, and can best send blood to the parts essential in the run or the fight for life, is most likely to survive. Such, according to the view here propounded, is the function of the adrenal medulla at times of great emergency.[3]

[1] *See* Hoskins and McClure: *Loc. cit.*, p. 353. Cannon and Lyman: *Loc. cit.* p. 376. [2] *Cf.* Elliott: Journal of physiology, 1904, xxxi, p. xx.

[3] Since this paper was prepared Dr. W. L. Mendenhall and I have found that splanchnic stimulation may greatly hasten the coagulation of the blood. This result does not occur if the adrenal gland has been removed on the side stimulated. Thus excitement and pain, through the agency of the adrenal medulla, may be serviceable to the organism in preventing loss of blood in case of vascular injury. The pertinence of these observations to the view presented in this paper is obvious.

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ON THE PERCENTILE MEASUREMENT OF THE VASOMOTOR REFLEXES

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PRIOR to 1907 when an afferent vasomotor nerve, for example the sciatic, was stimulated, the resultant change in blood pressure was measured by the extent to which the blood pressure rose above the level at which it stood just before stimulation. This may be called the absolute change in blood pressure. In 1907 it was proposed [1] that the criterion be not the absolute but the percentile change, i.e., that the observed rise or fall be divided by the blood pressure at the beginning of stimulation.

A correct choice between the absolute and the percentile method of reckoning is of the highest importance, because this choice determines quantitatively the normal reflex and such a reflex is the only evidence that the vasomotor apparatus is normal.

The present communication will demonstrate that when the initial blood pressure stands between about 20 and about 90 mm. Hg and the vasomotor nerves are stimulated, the resultant changes in the blood pressure must be measured by the percentile and not the absolute value. Under these conditions, only the percentile value will enable the observer to form correct conclusions regarding the state of the vasomotor apparatus.

The data to be presented are from experiments on cats and rabbits performed from Nov. 6, 1906 to April 4, 1907, and from Sept. 28 to Oct. 23, 1907. The experiments of the first period

[1] W. T. Porter. This journal, 1907, xx, p. 402; also 1908, xxi, p. 461, and xxiii, p. 132.

were made to determine the effect of hemorrhage on the vasomotor reflexes; those of the second period were part of a study of the vasomotor reflexes in animals of different species; neither investigation was concerned with the problem now in hand.

The blood pressure in these experiments varied naturally or was made to vary by withdrawing small amounts of blood. These amounts were often defibrinated and replaced by injection through the external jugular vein. None of the data used in this paper were taken from animals in which loss of blood had weakened the vasomotor centre. The intervals during which the blood pressure was experimentally lowered were much too short to affect the nutrition of the vasomotor cells. That the vasomotor apparatus actually remained in its usual state was shown by restoring the blood pressure to its usual level and obtaining then the usual (absolute) reflex upon stimulating the sciatic, the brachial, and the depressor nerves.

It being established that the vasomotor arc was normal, it follows that only the reflex that showed this normal state can be correct, and that a reflex indicating an abnormal condition of the vasomotor arc must be misleading.

The result [1] of this enquiry is shown in Table I. It is seen that when the afferent nerves were stimulated at initial pressures varying from 90 to 20 mm. Hg, the absolute resultant change in pressure sank steadily, from which we should be obliged to conclude that the vasomotor arc became progressively incompetent. But the percentile reflex remained almost unaltered. Since it was known that the vasomotor arc remained at its normal level of efficiency, it is obvious that between the initial pressures 90 to 20 mm. Hg [2] the percentile method of measuring the reflex is correct and the absolute method incorrect.

[1] The individual measurements are given in Tables II and III.

[2] At levels above 90 mm. the arteries are so distended that the percentile reflex diminishes. At these high levels the state of the vasomotor cells can probably be determined with the aid of a curve to be constructed from a great number of measurements. It should be observed that in practice the state of the vasomotor centre is seldom a matter of concern when the blood pressure is high. It is precisely when the blood pressure is at the levels measured in this present investigation, as for example in "shock," that correct conclusions regarding the vasomotor arc become essential.

TABLE I

THE PERCENTILE CONTRASTED WITH THE ABSOLUTE CHANGE IN BLOOD PRESSURE ON STIMULATING THE SCIATIC, BRACHIAL, AND DEPRESSOR NERVES.

Nerve	Initial Pressure	Percentile Change	Absolute Change
	Mm. Hg	Per Cent	Mm. Hg
Sciatic	70 to 89 mm. Hg.	73	53
	50–69	74	48
	30–49	70	25
	20–29	73	18
Brachial	70 to 89	69	51
	50–69	68	40
	30–49	67	26
	20–29	64	12
Depressor	70 to 89	36	27
	50–69	32	17
	30–49	30	10
	20–29	—[1]	—[1]

[1] Omitted for lack of a sufficient number of observations.

TABLE II

THE ABSOLUTE CHANGE IN BLOOD PRESSURE ON STIMULATING THE SCIATIC, BRACHIAL, AND DEPRESSOR NERVES.

20 to 29 mm.			30 to 49 mm.			50 to 69 mm.			70 to 89 mm.		
Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.
25	20		25	30	13	15	43	25	30	70	35
20	18		30	30	10	40	60	20	74	48	30
21	20		13	30	8	46	30	15	60	40	30
21	6		65	30	7	65	30	21	40	52	15
21	8		10	20	12	62	26	10	25	54	24
22	14		25	25	13	51	44	20	40	44	30
10	13		20	35		66	35	12	52	40	14
8	14		25	15		58	38	16	58	58	14
	12		42	15		30	56		38		20
	5		20	20			30		58		24
	5		45	34			45		65		30
			20	9			40		76		24
			20	23			64		51		48
			18	15			26		80		36
			9	35			32				
			11	42			36				
			25	28							
			49	26							
			32								
			43								
			33								
			8								
			9								
			40								
			7								
			12								
18	12	—	25	26	10	48	40	17	53	51	27
Averages											

TABLE III

THE PERCENTILE CHANGE IN BLOOD PRESSURE ON STIMULATING THE SCIATIC, BRACHIAL, AND DEPRESSOR NERVES.

20 to 29 mm.			30 to 49 mm.			50 to 69 mm.			70 to 89 mm.		
Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.	Sc.	Br.	Dpr.
%	%	%	%	%	%	%	%	%	%	%	%
95	100		56	75	34	50	78	45	100	100	47
43	90		100	75	33	23	100	33	75	69	38
100	100		43	100	25	67	50	30	50	48	38
100	30		144	100	23	94	60	36	36	69	35
84	29		33	67	30	130	43	17	57	78	30
84	70		71	63	33	97	70	40	70	59	53
84	65		50	78		93	70	24	67	48	20
37	64		26	45		66	62	27	54	82	22
31	71		55	50		94	93		77		28
	50		93	50		30	54		87		31
	36		50	56			75		67		39
			100	27			69		107		30
			50	75			110		70		54
			50	48			48		100		43
			53	78			50				
			25	100			53				
			53	58							
			104	54							
			100								
			134								
			89								
73	64	—	70	67	30	74	68	32	73	69	36
Averages											

FURTHER OBSERVATIONS ON THE RATE AT WHICH SUGAR DISAPPEARS FROM THE BLOOD OF EVISCERATED ANIMALS

By J. J. R. MACLEOD and R. G. PEARCE

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SINCE the publication, some months ago, of a series of observations bearing on the rate at which sugar disappears from the blood of normal and diabetic dogs after removal of the abdominal viscera, several sources of error that might possibly have interfered with the accuracy of the results have presented themselves. In the present communication are offered the results of further experiments of a similar nature, but in which precautions were taken to avoid these errors.

Although the main conclusion drawn from the previous series of experiments, namely, that there is no appreciable difference in the rate with which sugar disappears from the blood in diabetic as compared with normal animals, has since been confirmed by Patterson and Starling[1] for perfused heart-lung preparations, yet we have thought it advisable to place on record our later results if for no other reason than to show that even when the diabetic state has persisted for over a week, there is no evidence of depressed glycolytic power in eviscerated animals. This conclusion is at variance with the assertion of Verzar[2] that sugar injections do not cause an increase in the respiratory quotient in dogs from whom the pancreas has been removed for more than four days, although such injections do cause a marked increase in the quotient in normal animals.

In the present series of observations the following extra pre-

[1] Patterson, S. W. and Starling, E. H.: Journal of physiology, 1913, xlvii, p. 137.

[2] Verzar, F. and Fejer, A. V.: Biochemische Zeitschrift, 1913, liii, p. 141.

cautions have been taken in performing the evisceration experiments:

1. Using decerebrated animals so that all chances of interference with glycolysis on account of the presence of anaesthetics in the blood might be avoided.

2. Making observations on the percentage of haemoglobin in the blood so as to ascertain to what extent this might be undergoing dilution on account of absorption of fluid from the tissues.

Adopting these precautions, a series of observations was first of all made on several normal animals in the hope that more constant results than those previously published might be secured, with which could be compared not only the glycolysis occurring in diabetic animals, but also that occurring after the administration of adrenalin in normal animals. As the table depicting the results of five such experiments shows, the glycolysis expressed as milligrams of dextrose disappearing from 100 gr. blood per minute varied from 0.47 to 1.8. In no case could more than a small proportion of this disappearance be attributed to dilution of the blood by tissue fluid, this being shown in the sixth column where the percentile dilution of the blood is computed from (1) Hb, (2) decrease in sugar percentage.

With such irregularity in the results, it is obvious that only the most extreme degrees of change in the glycolytic power could be expected to reveal themselves. Any further attempt to investigate the possible influence of adrenalin on the glycolysis was therefore abandoned.

Two experiments were, however, conducted on dogs from which the pancreas had been completely removed eight days previously. The animals were fed on moderate amounts of flesh and gave D : N ratios indicating a marked degree of diabetes. During the evisceration experiments on these diabetic dogs it was necessary to give some adrenalin because the animals were in a depressed condition and it was impossible otherwise to maintain an adequate blood pressure. The results show a more marked degree of glycolysis than normal, which is very probably due to the stimulating influence of the adrenalin on the activity of the heart.

The irregularities in rate of glycolysis which we have found

TABLE I

SUGAR CONSUMPTION IN NORMAL AND DIABETIC EVISCERATED AND DECEREBRATED DOGS

Normal Dogs

No. of expt. / Weight	Time after evisceration (minutes)	Percent dextrose in blood	Mg. dextrose disappearing from 100 gr. blood per min.	Percent Hb	Percent increase in vol. of blood as calculated from: (1) sugar, (2) Hb	Remarks
(1)	(2)	(3)	(4)	(5)	(6)	(7)
I	Immediately	0.066				Starved. Spec. grav. of blood constant. Decerebrate rigidity. B. P. well maintained
	20	0.063				
17 Kg.	40	0.045	0.9			
	60	0.035	0.47			
	80	0.013	1.12			
III	17	0.132		90	Sugar 37	[1] B. P. very low. Rigidity not marked
	37	0.096	1.8	83	Hb 8	
15 Kg.	57	0.083 [1]	0.6			
IV.	6	0.209		90	Sugar 23	
13 Kg.	33	0.170	1.4	86	Hb 5	
V	Immediately	0.129		84	Sugar 116	
	20	0.078			Hb 16	
7.9 Kg.	40	0.060	0.91	72		
VII	Immediately	0.257		100	Sugar 29	Adrenalin injected after 20 minutes
	20	0.222	1.75	84	Hb 18	
11.4 Kg.	42	0.199	1.04	86		
	62	(0.203)	—	—		

TABLE I (*continued*)

Diabetic Dogs

No. of expt.	Time after evisceration (minutes)	Percent dextrose in blood	Mg. dextrose disappearing from 100 gr. blood per min.	Percent Hb	Percent increase in vol. of blood as calculated from: (1) sugar, (2) Hb	Remarks
(1)	(2)	(3)	(4)	(5)	(6)	(7)
VIII	Immediately	0.296				8 days after pancreatectomy D:N ratio 2.0 adrenalin
	25	0.212	3.36			
IX	Immediately	0.265		100		8 days after pancreatectomy D:N ratio 2.7. Decerebrate rigidity. Adrenalin
	30	0.207	1.9	92	Sugar 28 Hb 8	
	55	0.140	2.68	84	Sugar 47 Hb 8	

are probably dependent upon irregular consumption by the muscles of the glycogen which is stored within them. In the diabetic animal, as Cruickshank[1] has recently shown, the source of this glycogen may be partly the heart itself. We believe that these irregularities in sugar consumption, not only in our experiments, but also in those on the perfused heart-lung preparation, make it impossible by such methods to arrive at any conclusions as to whether dextrose is any less easily burnt in diabetic as compared with normal animals. Experiments in which the behavior of the respiratory exchange is observed, such as those recorded by Murlin[2] are of much greater value.

[1] Cruickshank: Journal of physiology, 1913, xlvii, p. 1.

[2] Murlin: The journal of biological chemistry, 1913, xv, p. 365.

SOME FACTORS CONTROLLING THE SHAPE OF THE PRESSURE CURVE IN THE RIGHT VENTRICLE[1]

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I. Previous Work

THE controversy as to the correct shape of the intraventricular pressure curve is too well known to demand again an extensive review of the older literature.[2] Briefly recalled, opinions differed as to whether the steep systolic ascent is followed by a flat plateau or a rounded top imperceptibly merging into the descending limb.

So complex and rapid are the pressure changes and consequently so great become the requirements of manometers for their accurate registration that a final direct analysis seemed to some impossible in the rapidly beating mammalian heart. Accordingly, Frank[3] in 1895 sought to approach the subject by studying the isotonic and isometric contraction curves of the frog's heart and the afterloaded curves which resulted when the heart was placed in connection with an artificial circulation scheme. Since the conclusions are of importance in analyzing records obtained from mammals, they may be briefly recalled. Frank found that the height of the isometric pressure curve (obtained by preventing both ventricular outflow and inflow during systole) and, to a certain limit also, the steepness of its ascent increased directly with the initial tension, i.e., the degree of diastolic filling. On

[1] The third of a series of studies on the pulmonary circulation, the previous papers of which were published in this journal, 1912, xxx, p. 233, and 1914, xxxiii, p. 1.

[2] For excellent reviews of the literature see Hill; Schäfer's textbook of physiology, 1900, ii, 18; Tigerstedt: Skandinavisches Archiv für Physiologie, 1912, xxviii, p. 36.

[3] Frank: Zeitschrift für Biologie, 1895, xxxii, p. 370.

the other hand, the height of the isotonic curve, which is proportional to the discharge, decreased with an increase in load. In the afterloaded curve obtained by allowing the heart to eject blood into an artificial system composed of glass tubes but containing also a controllable elastic factor, three phases are recognizable, namely, (1) the period of rising tension (Anspannungszeit), (2) the period of ejection, and (3) the period of relaxation. In the first period, terminating with the opening of the semilunar valves, the curve obeys the law of isometric contraction as far as the incline of its rise is concerned, but its height is modified by the height of the aortic pressure as well as by the initial intraventricular pressure. During the second period the curve rises less rapidly, reaches a summit, and, when the rate of arterial inflow is exceeded by the outflow, the pressure begins to descend in a manner corresponding with that in the aorta, with which the ventricle now forms a common cavity. To this portion of the record, consisting of ascending and descending limbs, the term "plateau," could be applied, but Frank discourages such a terminology since the untenable idea has come to be associated with it, that the pressure remains parallel to the abscissae during this interval.

Such hemodynamic experiments can only be used to forecast the nature of the mammalian intraventricular pressure curve provided it is assumed with Frank that the frog's ventricle beats after the fashion of mammalian hearts. In view of the complicated arrangement of the cardiac musculature in mammals,[1] however, some physiologists would not assent to such an assumption. Consequently, it is desirable to institute mammalian experiments with manometers capable of accurately following the pressure changes within the heart cavities.

By formulating the fundamental guiding principles in manometer construction, Frank[2] has also contributed the essential means for a direct solution of the problem. Thus Straub,[3] Piper,[4] and Tigerstedt[5] all used optically recording instruments of high

[1] Mall: The American journal of anatomy, 1911, ii, p. 211.
[2] Frank: Zeitschrift für Biologie, 1903, xliv, p. 445.
[3] Straub: Archiv für die gesammte Physiologie, 1911, cxliii, p. 69.
[4] Piper: Archiv für Physiologie, 1912, p. 343.
[5] Skandinavisches Archiv für Physiologie, 1912, xxviii, p. 36.

vibration frequency, whose construction was made possible on the basis of Frank's analysis alone.

Records so obtained have, however, already received different interpretations. Thus Straub described the intraventricular pressure curve as an exceedingly simple curve, evenly rounded at its top and free from sharp secondary vibrations. Piper, on the other hand, described his curves as displaying a rapid rise topped by a few short vibrations and followed by a broadly rounded plateau terminating in an uneventful fall. C. Tigerstedt corroborated the findings of Piper in the left ventricle. His curve, in addition to the superposed vibration at the beginning of the ejection period, gave evidence of a sharp change in the descending limb due to closure of the aortic valves. The top, according to this investigator, may be described as a plateau which is ascending, horizontal, or descending in accordance with the resistance ahead.

In a preliminary communication, the writer[1] pointed out that all optically recorded curves contained certain features in common, but that the general appearance of the records was determined largely by the sensitiveness and damping of the manometer and the speed of the bromide surface. A more careful analysis of a larger number of records shows that other factors may be introduced which account for variations in contour. These were accordingly studied and make the basis of this report.

II. Apparatus and Technic

In order to record the pressure curve within the right ventricle correctly it is necessary to employ a manometer of high vibration frequency, and in order to obtain correct quantitative curves it is important to keep the cannula free from a coagulum and to keep the instrument approximately aperiodic for the pressure changes involved. A new manometer meeting the demands both of accuracy and convenience was therefore devised.

It consists (Figs. 1 and 2) of a vertical glass tube (*A*) surmounted by a hollow brass cylinder (*B*). This contains a stop-

[1] Wiggers: Proceedings of the society for experimental biology and medicine, 1913, xi, p. 11.

cock (*C*) with a conical lumen, the truncated cone of which comes into apposition with a damping plate (*a*) having an opening 2 mm. in diameter. By giving the stopcock a slight turn the instrument can be rendered almost aperiodic to suit any membrane or any pressure change by increasing the damping practically at one point. Above the damping plate the cylinder ends in a segment capsule (*b*) (3 mm. in diameter) covered with rubber dam. Upon

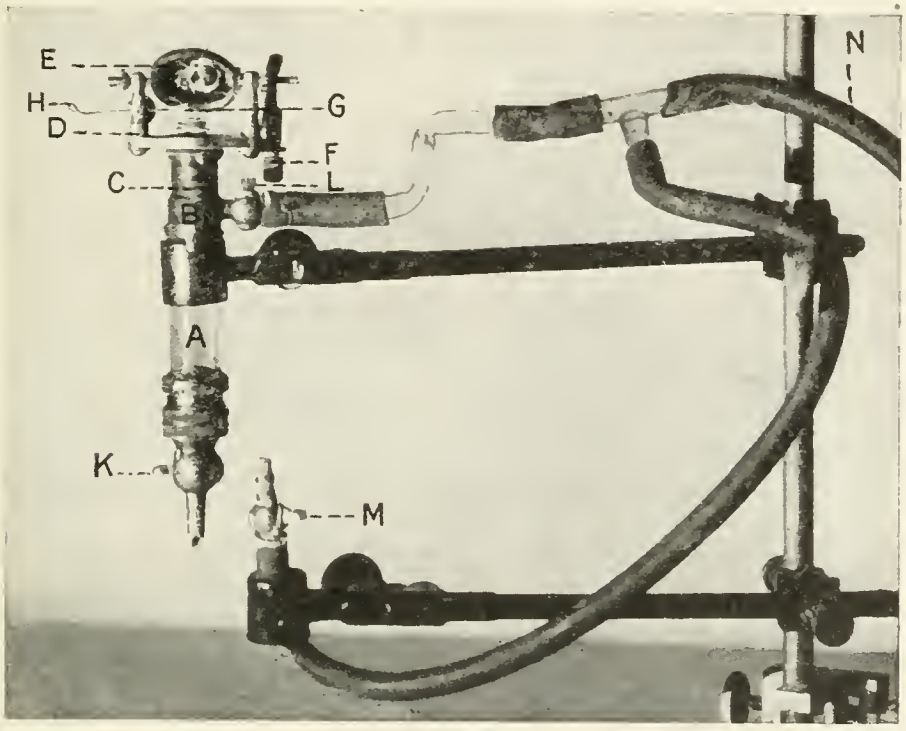

FIGURE 1. Optical manometer, letters referred to in text.

this a small piece of celluloid carrying a little Zeiss mirror (2 x 4 mm.) (*c*) is fastened so that it pivots on the chord side of the segment capsule. Over the segment capsule and its recording mirror is mounted a support (*D*) bearing an inclined reflecting mirror (*E*) adjustable about an horizontal axis by a screw (*F*) so that the image of the recording mirror appears within it. Upon this image the band of light from a Nernst or an arc light is focused. The incident rays are doubly reflected as shown in the diagram of Fig. 2.

For quantitative work the instrument is calibrated with reference to a streak of light projected by a second small mirror (*G*) fastened to one arm of the support and adjusted to the side

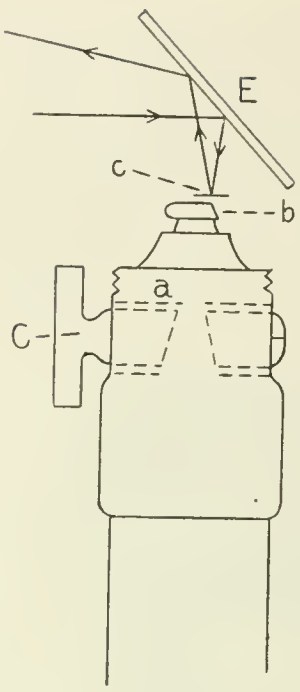

FIGURE 2. Diagram of optical manometer showing internal structure and light reflection. Letters referred to in text.

slightly above the recording mirror, so that it divides the light with the movable mirror and reflects it along a similar path. The distance between the two bands of light thus projected over one another on the recording camera can be adjusted by rotating the small rod (*H*) supporting the calibrating mirror.[1]

The lower end of the manometer is fitted by a conical joint with one of several styles of cannulas. For direct insertion through the ventricular musculature the straight, pointed, and slightly conical cannula (*K*) shown in Fig. 1 was used. For introduction through the auricular appendage a short curved cannula guarded by a stopcock having the same lumen was used, and for introduction through the external jugular a longer cannula was employed. The dimensions of the cannulas and the vibration periods of each are given in the following table.

Type of cannula	Lumen mm.	Length cm.	Vibration rate per second .3 mm.[1]	.43 mm.[1]	1 mm.[1]	Calibration
Straight	4	3.4	100	114	157	2.2[2]
Short curved	3	7.3	50	71	83	1.9[2]
Long curved.....	3.5	12.3	50	66	71	1.1[2]

[1] Figures refer to thickness of membrane.
[2] Figures in column indicate the number of mm. in record equal to 1 mm. pressure change.

In calibrating the instrument, stopcock *K* is closed and stopcock *L* opened. By opening stopcock *M* and placing its outlet on a level with the opening of cannula *K*, the zero level is obtained at any time during an experiment. By closing stopcock *M* and introducing pressure through the tube *N*, communicating with a mercury manometer and pressure flask, one can obtain

[1] It should be stated in justice to the Munich laboratory of physiology, that although the details of construction differ essentially, the convenient principle of light reflection was taken from a manometer in use in Frank's laboratory in 1912 but not yet described.

any series of calibrations in relation to the fixed line given by the second small mirror (*H*).

The cannula is kept free from clots by introducing a few cubic centimetres of anti-coagulating fluid occasionally. The mean pressure may also be read at any time by closing stopcock *N* and opening stopcock *M*.

The technic of insertion is very simple. A direct introduction of the short straight cannula through the right ventricular wall is the procedure of choice, for in this way a normal valve action and a normal transmission of auricular pressure to the ventricle are insured. In this procedure the manometer does not interfere with cardiac movement or contraction, nor, on the other hand, does the cardiac movement jar the instrument materially if a point is selected for insertion where the heart muscle is affected neither by the descent of the base nor the rise of the apex. A window is cut in the pericardium over the area to be utilized. With sharp, pointed scissors a stab is made into the ventricular cavity and the cannula introduced before more than a single spurt of blood takes place. No leakage occurs around the conical cannula, for, aside from its close fit, the intraventricular pressure is very low during diastole and the fibres firmly contracted around the cannula during systole. The entire manometer is then rigidly clamped so as to be, itself, immovable.

The short curved cannula is inserted through the ear of the auricle when it is desired to apply a cardiometer simultaneously to the ventricle, and the long cannula is used only in experiments where it is desired to study the pressure changes in the closed chest.

Right auricular pressure was, as a rule, read by a water manometer introduced through the jugular vein. Carotid or pulmonary arterial pressures were simultaneously recorded in selected experiments.

III. Types of Intraventricular Pressure Curves and their Determining Factors

The Normal Curve. — An intraventricular pressure curve, obtained when right auricular pressure and pulmonary arterial

pressure are approximately those found in naturally breathing animals, may be regarded as a *normal type* in open chest experiments. An "effective" auricular pressure of 45–50 mm. of water and a mean pulmonary arterial pressure of 18 mm. Hg may be regarded as normal averages.

In eleven experiments, such pressure combinations were obtained by a low degree of pulmonary ventilation. A few typical waves are shown in Fig. 3.

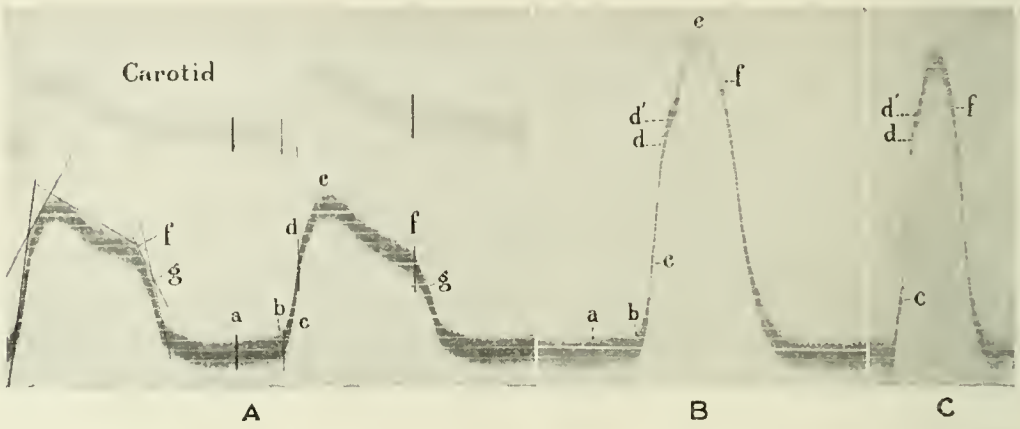

FIGURE 3. Three types of normal intraventricular pressure curves taken with manometers of different degress of sensitiveness. Detailed description in text. *a–b*, auricular systolic, *b–d*, isometric period, *d–f*, ejection period, *f–l*, diastole. Calibration line cut off.

The record in *A* was taken with a manometer in which a variation of 1 mm. was approximately equal to a like pressure change in the ventricle. The details of this curve are clear. Auricular contraction causes the slight rise of pressure from *a* to *b*. The tricuspid closure occurs in the confused vibration at *c*. The steep pressure rise during the *isometric period* (Anspannungszeit) follows from *c* to *d*. Here the semilunar valves open and the *ejection period* begins. This proceeds in two phases, viz., a rise of pressure (*d* to *e*) which is slower than that of the isometric period, changing after a rounded summit to the falling pressure (*e* to *f*). The closure of the semilunars causes the bend from *f* to *g*, after which the pressure drops rapidly in diastole. Attention may be called to the exact correspondence in contour between the ejection period and the arterial pressure curve upon which the corresponding relations are marked.

When the intraventricular pressure is recorded by manometers

in which 2 mm. of calibrated record represented approximately 1 mm. of intraventricular pressure change, the same details can be made out (Fig. 3, *B*). In these manometers there is a greater tendency to show superposed vibrations at the beginning of the ejection period (*d'*) and the closure of the tricuspid valves is also more clearly indicated. The two phases of the ejection period are still clearly recognizable. If, however, these records are recorded on slowly moving paper (Fig. 3, *C*) the existence of a broadened top is less clear to the eye. If, in addition, the manometer is damped, the jog at *d* is eliminated and a smoothly rounded curve similar to those of Straub is obtained. Close inspection still reveals evidences of all the angles illustrated in Fig. 3, *A*. (*Cf.* Straub's records.) Hence, while it may not be asserted that such records are wrong, it cannot be denied that they tend to obscure the details of the pressure variations as they actually exist and may readily lead to the erroneous conclusions formulated by Straub. Hence, whenever it becomes desirable to record such curves on slowly moving paper for special reasons, a careful scrutiny of the curve for its true details must not be neglected.

The Influence of Auricular Pressure on the Initial Intraventricular Tension and the Shape of the Pressure Curve. — Inasmuch as auricle and ventricle, during the diastole of the latter, are in free communication, it is commonly supposed that the intra-auricular and the *initial intraventricular pressures* (i.e., the pressure just before ventricular systole) are practically equal. Such is found to be the case when pressures are low. When, however, intra-auricular pressure increases, due to asphyxia or saline infusion, the initial intraventricular pressure deciphered from calibrated optical records (e.g., at *b*, Fig. 1), are progressively lower than auricular pressures measured by the water manometer.[1] The results, belonging to the curves shown in Fig. 4 and indicated in the following table in millimetres of water, are characteristic.

Intra-auricular pressure	24	32	54	90	130	150	190
Initial Intraventricular pressure	23.1	26.9	34.6	61.6	81.6	106.1	115.5

[1] For technic of measurement, *cf.* WIGGERS: This journal, 1914, xxxiii, p. 15.

Further experiments will be necessary to determine whether this may be attributed to the inferiority of a saline manometer in measuring these changes. For the present it is sufficient to direct attention to the fact that the figures of intra-auricular pressure given by the convenient saline manometer may not always be regarded as synonymous with the initial intraventricular tension.

The effect of changing the initial intraventricular tension[1] is exemplified by the transcribed curves shown in Fig. 4. As

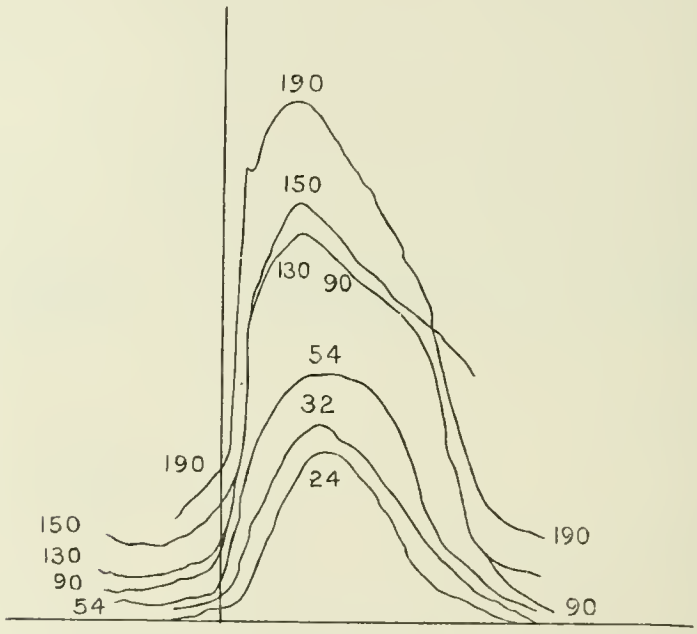

FIGURE 4. Effect of initial auricular pressure on initial tension and pressure curve. Numbers refer to auricular pressure.

the auricular and, consequently, the initial intraventricular pressure increased, the entire curve mounted higher. The steepness of the ascending limb increased, showing that it follows the law of the isometric curve established by Frank for[2] the frog's ventricle. The height of the isometric portion of the curve (i.e., the point *d*, Fig. 3), as in the case of the afterloaded frog's ventricle, is determined not only by its incline, but by its termination through opening of the semilunar valves.

[1] Lower pressures were produced by clamping the inferior vena cava or hemorrhage; higher pressures, as a rule, by saline infusion.

[2] FRANK: *loc. cit.*

The curves undergo a marked change in contour during the ejection period. With low initial pressures the top is quickly reached and the descending limb of the ejection period merges almost imperceptibly with the diastolic fall, giving the curve a simple rounded contour. As the initial pressure approaches normal, the top becomes broadened and more clearly divisible into its ascending and descending limb. This continues with very high auricular pressures.

Influence of Pulmonary Resistance. (*a*) **Clamping Pulmonary Vessels.** — By suddenly drawing tight a ligature previously placed around a large pulmonary branch, the resistance in the main pulmonary artery should be increased.

Previous investigators [1] have found such an increase in resistance of no recognizable importance for the intraventricular pressure. The curves of Fig. 5 indicate, however, that the maximal

FIGURE 5. Effect of compressing lung vessel in the intraventricular pressure curve. Description in text.

pressure increases as the ligature is tightened. The initial tension remains unaltered and the steepness of the isometric period is consequently also unchanged, but the period ends progressively later as the compression continues.

The ascending limb of the ejection curve increases in height and reaches the summit later than before, that is, the peak is carried more toward the end of the ejection period. This indicates that the point at which the outflow exceeds the inflow of

[1] TIGERSTEDT: Ergebnisse der Physiologie, 1903, ii², p. 557.

the pulmonary artery occurs relatively later when the total resistance is increased.

(*b*) **Influence of Lung Inflation.** — In four experiments the lungs, entirely freed from their pleural attachments, were inflated to four degrees that may be described by the terms, (*a*) forcibly collapsed, (*b*) naturally collapsed, (*c*) mildly inflated, (*d*) strongly inflated. In the intraventricular pressure curves taken during these respective stages of lung inflation, typical changes took place, three examples of which are given in Fig. 6.

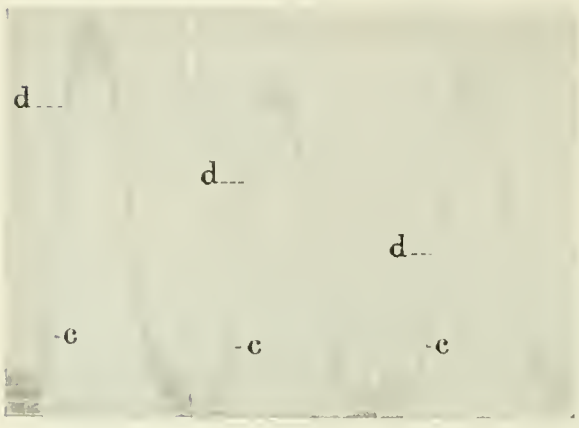

FIGURE 6. Three intraventricular pressure curves taken with (*a*) lungs naturally collapsed, (*b*) moderately inflated, (*c*) markedly inflated.

The initial intraventricular pressure and hence the steepness of rise remain unaltered. The isometric period terminates at a lower level when the lungs are most markedly inflated and within a shorter time interval. The greater the inflation, the more pointed the summit; or, vice versa, the more rounded top occurred when the lungs were collapsed.

Comparing these records with those obtained by compressing the lung vessels the conclusion appears obvious that the *resistance in the pulmonary circuit decreases when the lungs are inflated*, and increases when they collapse. Attention may be briefly directed to the fact that this is contrary to current teaching as to the influence of lung inflation, but accords with the recent observations of Cloetta.[1]

Influences Modifying the Contractility of Cardiac Muscle. — It is obvious that any mechanism modifying the function of cardiac contractility may, independent of initial pressures and pulmonary resistance, modify the shape of the intraventricular pressure curve. Since such an action may occur as a result of therapeutic or pathological influences, and, probably, normally as well, it is important to study the nature of the influence.

[1] CLOETTA: Archiv für experimentelle Pathologie und Pharmakologie, 1911, lxvi, p. 409.

It was sought at first to test the influence of the vagus in this capacity. As a result of such stimulation it was found that all the results can most probably be explained as resultants of a changing initial tension and pulmonary arterial pressure. Inasmuch as not a sufficient number of experiments are at hand to rule out the possibility of such an influence occurring in unanaesthetized animals, they are not incorporated in this report.

Contractility may be conveniently modified by two internal secretions however. It may be augmented by adrenalin and depressed by pituitary extract.

(*a*) **Effect of Adrenalin.** — If adrenalin is introduced while the intraventricular pressure curve is recorded on a film that moves relatively slowly, it is found that, synchronously with the increase in rate, a reduction of the initial intraventricular pressure and an increase in the height of the curve take place. The *a–v* valves close at a somewhat lower intraventricular pressure, but the semilunar valves open only when a higher level is reached. The isometric period shows a steeper rise and occupies a shorter time *contrary* to what might be anticipated were the lower initial pressure alone concerned. It can only be inferred, therefore, that adrenalin directly modifies the contractility. After eight or ten beats the acceleration is superseded by a vagal slowing. The initial pressure becomes still lower, but the contractility effect keeps on increasing.

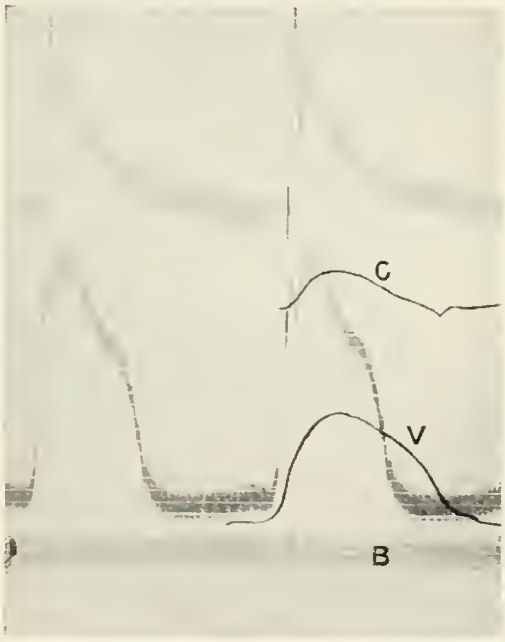

FIGURE 7. Comparison of the intraventricular and carotid after adrenalin compared with the same (sketched in) before.

These details of contour may also be discerned in the record of Fig. 7, over which (but relatively too near the base line) has been traced the curves *c* and *v* representing the respective carotid and intraventricular curves before adrenalin administration, They show clearly, furthermore, that whether or not vibrations

occur at the beginning of the ejection period and in the aorta depends largely upon the vigor with which the heart contracts and, since they are found normally in the carotid and pulmonary arterial pressure curves, it may be assumed that they occur also within the ventricle in the unopened chest. Unquestionably, as here, the depressing effect of anaesthetics and exposure of the heart may completely abolish these superposed vibrations from experimental records. Hence, the writer would not regard records such as are shown in Fig. 3, *A* — even when venous and arterial pressures are adequate — as entirely representative of those occurring normally, but as curves from a depressed heart. Only those

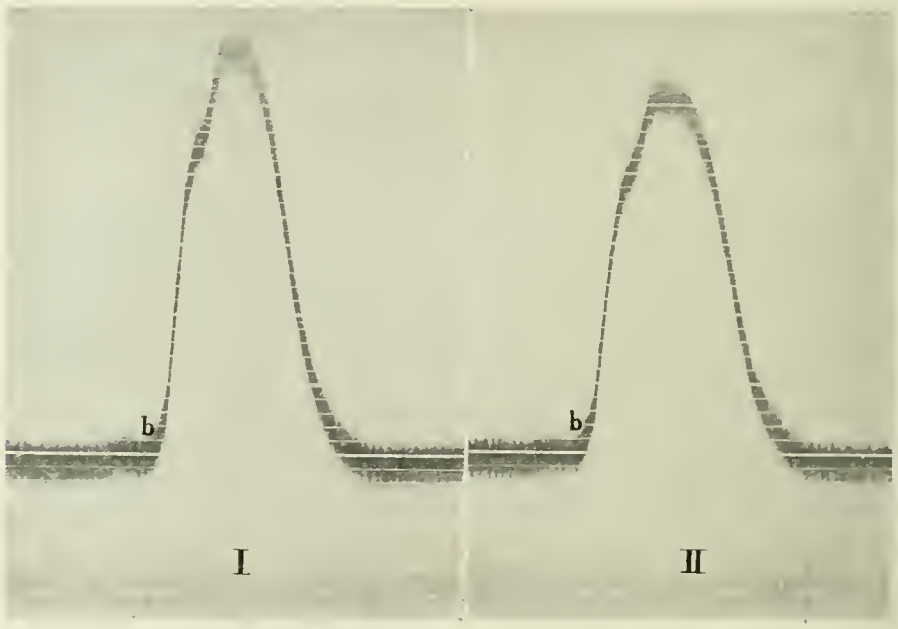

FIGURE 8. Two curves of intraventricular pressure before (I) and after (II) pituitary extract.

intraventricular pressure curves displaying oscillations at the beginning of the ejection may be regarded as showing normal contractility (e.g., Fig 3, *b*). Such curves only should be made the standard in studying pathological disturbances experimentally.

(*b*) **Effect of Pituitary Extract.** — The writer [1] has previously shown that pituitary extract, unlike adrenalin, decreases the amplitude of cardiac contractions. Inasmuch as this is contrary

[1] WIGGERS: American journal of the medical sciences, 1911, cxli, p. 508.

to the results obtained by Hedbom[1] and, more recently, by Werschinin,[2] its effect in intraventricular pressure is of interest. Two waves, one before, the other after pituitary action, are shown in Fig. 8. Synchronous with its slowing action it causes a decrease in the height of the pressure curve. In spite of an increase in the initial intraventricular tension measured at *b* the steepness of the isometric curve decreases and terminates at a lower pressure.

IV. Summary

1. When the auricular and pulmonary arterial pressures are approximately normal the pressure curves in the right ventricle, recorded by optical manometers of high vibration frequency, may be divided into (1) an auricular period, (2) an isometric period (period of rising tension) (3) an ejection period, during which the pressure rises, reaches a summit, and then slowly falls, and (4) a relaxation period (Fig. 1).

2. The *initial intraventricular tension*, i.e., the tension existing in the ventricle just before contraction, is not as great as auricular pressure when the latter is high, but, as both increase in the animal, the isometric curve becomes steeper and terminates later. The ejection period changes from a rounded to a broadened top with a higher summit and a clearer differentiation into an ascending and descending limb.

3. Increasing the pulmonary resistance by occluding a pulmonary branch causes an alteration neither in the initial tension within the right ventricle nor in the steepness of the isometric period, but prolongs this period of rising tension and causes a more rounded top in which the maximum is reached at a later time. As collapse of the lungs causes precisely the same changes as occluding the lung vessels, the deduction is made that *inflation of the lungs decreases and collapse increases the resistance in the pulmonary circuit.*

4. By modifying the contractility of the heart through adre-

[1] Hedbom: Skandinavisches Archiv für Physiologie, VIII, pp. 161–612, 1898.

[2] Werschinin: Ueber die Herzwirkung des Pituitrins, Archiv für die gesammte Physiologie, 1913, clv, p. 1.

nalin and pituitary extract and comparing these records with those obtained from deeply and lightly anaesthetized animals, the conclusion is arrived at that the presence and character of the superposed vibrations at the beginning of the ejection period, as well as those in the arteries, depend on the vigor of cardiac contractions. As the carotid and pulmonary arterial curves obtained with closed chest give evidence of such vibrations, they must also exist in the ventricle of unoperated animals. Such curves must, therefore, alone be regarded as entirely normal intraventricular pressure curves in spite of the fact that records free from them may be recorded when venous and arterial pressures are ostensibly normal.

THE NATURE OF FIBRILLARY CONTRACTION OF THE HEART.—ITS RELATION TO TISSUE MASS AND FORM[1]

By WALTER E. GARREY

[*From the Physiological Laboratory of Washington University, St. Louis.*]

IT is a noteworthy fact that the hearts (ventricles) of large animals fibrillate with great ease and only rarely recover from the fibrillary state, while small hearts rarely fail to recover. It was noted by McWilliam[2] that "spontaneous recovery may take place readily in the hearts of the cat, rabbit, rat, mouse, hedgehog, and fowl." The ventricles of dogs do not usually recover spontaneously from fibrillation, although they do so in rare instances, as noted by Porter.[3] The larger beef heart is one which enters into the fibrillary state with greatest ease and caprice. Erlanger[4] records this fact and states "that it is not often that fibrillation of the calves' heart can be stopped, as in other hearts, by means of temporary perfusion with potassium chloride solution." In this connection we may also refer to the well-known fact that fibrillation of the thin walled auricles is usually of a transitory nature, while that of the thicker ventricles of the same heart is much more prone to persist. It would appear obvious, from a consideration of these facts, that the size of the tissue masses involved in the process may have an important bearing on the induction of and recovery from the fibrillary state, yet, so far as we have been able to ascertain, these phenomena have never been systematically investigated from this viewpoint,

[1] The main features of this work were reported to the St. Louis Medical Science Club, November 12, 1912, and a synopsis appears in the Proceedings of the Society, Interstate medical journal, December, 1912, xix, p. 1081.

[2] J. A. McWilliam: Journal of physiology, 1887, viii, p. 296 *et seq.*

[3] W. T. Porter: This journal, 1898, i, p. 80.

[4] J. Erlanger: This journal, 1912, xxx, p. 400.

although Porter[1] found that he could suppress fibrillation of pieces of the heart more easily than the whole heart, and McWilliam[2] found that the isolated ventricular apices of all mammals worked with could recover from fibrillation again and again.

Our investigations give substantial support to the a priori view, based upon the above mentioned facts, that the ease with which the fibrillary process may be induced and with which spontaneous recovery from the fibrillary contractions takes place is inversely proportional to the mass of fibrillating tissue. In harmony with these facts is the finding that the extension of fibrillary process from any portion of the heart to another is dependent upon the cross sectional area of the conducting tissue connecting them. Our experiments support Porter's view that the essential nature of fibrillary contractions must be referred to abnormalities in impulse conduction — to the existence or establishment of blocks, or at least to relative differences in conductivity,[3] rather than to any peculiarity or alteration of contractile properties.

I. Experiments with Fibrillating Auricles

Any Small Auricular Piece will Cease Fibrillating. — When the auricles of cats, rabbits, or dogs are stimulated with strong faradic shocks, localized at any point, the whole musculature of both auricles enters into violent fibrillary contractions which usually persist for a time varying from a few seconds to several minutes, or more rarely for hours, after stimulation has ceased. In experiments conducted upon these mammals it was found that when a portion of the wall of fibrillating auricles was picked up by forceps and functionally separated from the heart by ligating, or by clamping with haemostatic forceps, the portion so separated ceased fibrillating at once, although the organ from which it was removed continued its inco-ordinated contractions unaltered. Such

[1] W. T. Porter: This journal, 1898, i, pp. 71–82.

[2] J. A. McWilliam: *loc. cit.*, p. 301.

[3] The block hypothesis originated with W. T. Porter: The journal of physiology, 1894, xv, p. 135; This journal, 1899, ii, p. 129; 1905, xiii, pp. xxiii and xxiv; 1905, xv, p. 5.

a procedure is especially applicable to the auricular appendices, and it was found that a whole appendix, either right or left, could be functionally removed in this way and would invariably stop fibrillating and come to complete rest. The appendices or other pieces could, subsequently, be removed by section and their properties studied.

The Excised Pieces Retain their Normal Properties.—It was important to determine whether pieces cut away from the fibrillating auricles had, as a result of their previous abnormality and removal from the heart, lost any of their physiological properties. It was found that they responded with a single normal co-ordinated contraction in response to a single mechanical or electrical stimulus. When the stimuli were repeated regularly a rhythmic response was elicited. Many of the pieces removed in the above experiments were immediately placed in warm (40° C.) sodium chloride solutions, or in Ringer's mixture, and all beat with perfect rhythms.

The normal functional capacity of the quiescent portions of the fibrillating auricles was strikingly illustrated by experiments of the following type: The heart of a dog was exposed and the auricles made to fibrillate by faradizing the tip of the right auricular appendix. The left appendix was then clamped off with a flexible intestinal clamp, the jaws of which were covered with rubber tubing. Compression was carefully graded to avoid any crushing injury and, as it increased in degree, fibrillation was seen to be supplanted by irregularly recurring co-ordinated contractions, the appendix finally coming to rest when block was complete. When the clamp was suddenly released, the appendix gave a few co-ordinated contractions and then fibrillated. These procedures could be repeated as many times as desired with the same results. The experiment became at once more striking and significant when the clamp was gradually released, for it was possible, in such cases, to obtain a degree of compression with which the appendix was kept beating in a perfectly co-ordinated manner, although irregularly. With further decompression these contractions passed over into a mere flutter and then fibrillation ensued. In two experiments the whole atrium assumed its normal rhythmic contractions while the clamp was in position and the appendix

was at rest; upon releasing the clamp the appendix beat as in partial block, later taking up the rhythm of the heart.

It is obvious from these experiments that pieces of auricular tissue possess normal capacity for rhythmic contractions when functionally separated from the fibrillating auricles. It is also clear that when connected normally they may fibrillate in response to an irregular shower of impulses which originate in the fibrillating auricular mass; when the number of these impulses is decreased by clamping, the piece may beat co-ordinately in spite of the inco-ordination of the auricular tissue with which it is connected.

The Fibrillary Contractions are not Sustained from the Point faradized in Initiating them. — Fibrillation has been looked upon as an inco-ordination which results from the fact that the irritability of certain areas is increased to such an extent that they become independently and highly rhythmic. In such a view the inco-ordination resolves itself into a response to extra-systole formation (Lewis).[1] Since faradization localized to a circumscribed area may precipitate the fibrillary process, it would seem logical to assume, as McWilliam[2] did, that the fibrillary contractions started in and were sustained from this area. This view would seem the more plausible since recent work has demonstrated that faradization of auricular tissue markedly increases its rhythmicity and force of beat (Erlanger).[3]

To test the validity of this idea of the nature of fibrillation a series of experiments was instituted to determine whether, after inducing fibrillation by stimuli localized within a very circumscribed area, the process persisted because impulses were continuously and inco-ordinately sent out from this area. The experiments were conducted along the lines of those described above. The tip of one auricular appendix was faradized until sustained fibrillary contractions were instituted, after which this appendix was functionally separated from the fibrillating auricles either by ligating, cutting, or clamping. As a result of this procedure the appendix came to rest, but the auricles invariably continued their delirium unaltered. The stimulated appendix behaved exactly

[1] Thos. Lewis: Heart, 1910, i, p. 353.

[2] J. A. McWilliam: *loc. cit.*, p. 309.

[3] J. Erlanger: This journal, 1910, xxvii, p. 102.

as any other portion of the auricles behaved when removed in a similar way.

Fibrillary contractions, then, are not dependent upon impulses initiated in any given area, even if the area be the one from which the process was started, but is a process in which the whole tissue mass is involved. It is dependent upon the integrity of a considerable mass of tissue, and subdivision of this mass into smaller bits brings all of the tissue out of the state of inco-ordinated contractions, the pieces either coming to rest or beating independently with a perfect rhythm depending upon the portion of the heart from which they were removed and upon the conditions to which they are subjected.

II. Experiments with Fibrillating Ventricles

Effects of Subdivision of Ventricles.—Any extended study of the relation of mass to fibrillary contractions is impossible with the hearts of cats or rabbits, owing to their well-known tendency to recover spontaneously from this condition, a tendency which may be due, at least in part, to their small size. It was determined, however, that cutting these small ventricles into two or four pieces would stop fibrillation immediately. More extended observations were conducted upon the ventricles of dogs, in which persistence of the fibrillary contractions is the rule. The results of subdivision of the ventricular tissue were independent of the cause inciting to fibrillation, i.e., whether the process was started by mechanical stimuli, by faradization, or spontaneously after the injection of digitalis, salts of barium and calcium, or other drugs.

Pieces were shaved from the wall of the fibrillating left ventricle by a cut parallel to the surface, the cut being so made that the cavity of the heart was not entered. These pieces ceased fibrillating at once, although some were two centimetres wide and four centimetres long, and as thick as could safely be made. In other instances the whole of the apices were removed by cut, clamp, or ligature after the manner described above for the auricular appendix. The piece thus removed always came to rest while the main fibrillating mass of the ventricles continued its abnormal

delirium. When pieces were cut away from the fibrillating ventricles it was noted that, like the apex, they ceased their incoordination and it was immaterial whether the pieces came from the walls of either ventricle or from the septum; they all behaved in identically the same way, provided they were of the same size.

It was noted, however, that larger pieces might fibrillate several seconds, or even half a minute after removal, while small bits ceased immediately. Pieces of equal surface area but including the whole thickness of the wall of the left and right ventricles, respectively, showed distinct differences in the time of persistence of the fibrillary contractions after removal; the thicker pieces taken from the left ventricle always fibrillated for a longer period before coming to rest. That the persistence of fibrillation is in direct proportion to the mass of the tissue is also indicated in the following type of experiment: Two cuts were made in the ventricle on either side of the septum and extending from the apex to the auriculo-ventricular ring, thus dividing the fibrillating heart into three pieces, the thin wall of the right ventricle, the thicker septal and left ventricular pieces. The two thick pieces continued to fibrillate, but the thinner right ventricle stopped within fifteen seconds. Additional cuts dividing each of the two fibrillating masses into two equal parts brought all the fragments to rest.

It was clear, from the numerous experiments made, that any piece cut from any part of the mass of ventricular tissue would cease fibrillating if small enough, e.g., if its surface area was less than four square centimetres. As was indicated for auricular tissue, even the portion to which the localized faradic stimuli had been applied in starting the fibrillary contractions could be excised and would come to rest while the remaining mass would fibrillate. A large part of the septum, when excised, acted in a similar way. Thus in the case of the ventricles, as with that of the auricles, fibrillation involves the whole tissue mass and is not dependent upon impulses coming from any single area of the tissue, nor is the recovery from the condition dependent upon any co-ordinating centre within the tissue (e.g., the septum), for any piece can recover.

Properties of Pieces Excised from Fibrillating Ventricles. — Quiescent pieces which have been excised from the fibrillating

ventricles of the dog are capable of responding with co-ordinated contractions when stimulated and will beat rhythmically when placed in warm M/6 solutions of sodium chloride. After recovery due to diminishing the size of the fibrillating mass, the pieces are also capable of responding to the normal physiological stimulus as the following experiment will indicate. By faradization the ventricles were made to fibrillate, in which process the auricles did not participate, but beat with their own rhythm, interrupted, however, by extra-systolic irregularities due to retrograde ventricular impulses. From the ventricles bits the size of a chestnut were removed piecemeal beginning at the apex. Each piece upon removal became quiet. When approximately three-fourths of the ventricle had thus been removed piecemeal, the remaining basal ring suddenly ceased fibrillating and beat in regular sequence with the auricles, indicating its return to relative normality. That, in this experiment, so large a mass of ventricle as one-fourth of the whole should have spontaneously ceased fibrillating may have been related to the fact that it was the basal portion with the shape of a ring (the importance of such a shape will appear in a subsequent section), or it may have been due in part to a slight cooling, which, as indicated by Porter's experiments, favors recovery; but the point of chief importance to us lies in the fact that so long as the mass was larger than one-fourth, fibrillation did not cease, while small pieces cut from it, and obviously of the same temperature, recovered immediately.[1]

[1] It should be emphasized that our method throughout has been one in which the relations of tissue mass and shape to the fibrillary contractions were determined upon tissues under like conditions; for example, the pieces compared had the same temperature as the fibrillating mass from which they were removed, yet they did not fibrillate. On the other hand the results were made doubly striking by the cessation of fibrillation in pieces which were transferred immediately to physiological saline solutions, the temperature of which was distinctly above that of the pieces. High temperatures have been shown by McWilliam (J. A. McWilliam: Journal of physiology, 1887, viii, p. 303) to increase the tendency to fibrillate. In our experiments, in which a clamp was applied to the auricle and alternately tightened and released to show cessation of fibrillation of the auricular appendix, and in similar experiments with ventricular tissue, as noted below, no question of differences in temperature can enter, and this is, of course, true in the experiments with the various turtle hearts.

In testing the reaction of pieces cut away in the above experiments faradic shocks were used in some instances. In these tests we obtained the significant result that very small pieces fibrillated only during stimulation, while larger pieces fibrillated for several seconds, or more, the duration of the fibrillary condition being in direct proportion to the mass of the tissue, emphasizing in another way the result obtained by the method of excision.

The Relation of Shape to Persistence of Fibrillation.—In performing the experiments described in the preceding paragraph, it was noticed that when faradic stimuli were applied to detached narrow strips several centimetres in length, the fibrillary contractions were confined to the region about the electrodes, but that the tissue at the other end of the strips beat co-ordinately, although irregularly. All contractions ceased when stimulation was stopped. This experiment suggested at once that fibrillation was impossible in sufficiently narrow strips.[1] This suspicion was at once justified when a fibrillating mass, such as the entire right or left ventricle or septum, was so incised as to make a trouser or trident preparation with individual parts connected by narrower bridges. Fibrillation ceased in such a preparation and faradization of one component always resulted in co-ordinate contractions of the other components. Similarly, it was found that when a cut was made into the apex of the fibrillating ventricles and continued spirally in such a manner as to produce a strip with a width of approximately one centimetre, the distal end of the strip would beat co-ordinately in response to irregular impulses coming from the fibrillating mass at its proximal end. It was possible to continue the incision and to progressively incorporate more and more of the fibrillating mass into the strip until, in some instances, it reached a length of thirty or even fifty centimetres. For a short time perfectly co-ordinate waves could be seen traversing the whole length of these strips. With the progressive reduction of the size of the fibrillating mass it was found that upon reaching a certain limit fibrillation ceased and beats, co-ordinate with the auricular contractions, intervened. The development of blocks in these strips will always take place sooner or later to interfere with the ideal picture just presented.

[1] J. Erlanger: This journal, 1910, xxvii, p. 99 *et seq.*

Owing to the rapid succession of impulses it is not always easy to determine whether the contractions of such strips are co-ordinated or not. Two procedures quickly revealed the true nature of the conditions; first, gentle compression of the proximal end of the strip established the condition of partial block and, by this means, the contraction waves could be made to progress down the strip with any desired intervals; second, single stimuli applied to the strip produced in it well-marked extra-systoles, which cannot be detected in fibrillating cardiac tissue.

In some instances success attended efforts to cut these strips, beginning at the apical portion of the ventricles, without precipitating the ventricles into the fibrillary state. The application of faradic stimuli to the strip produced inco-ordination in the region of the electrodes, but in no instance did this manipulation result in fibrillation of the ventricular tissue to which the strip was attached; it beat co-ordinately, rapidly, and with a surprisingly regular rhythm.

Conduction of the Fibrillary State.—It has been firmly established by the work of Vulpian and others [1] that in the mammalian heart the fibrillary state is not transmitted from fibrillating auricles to ventricles, or from fibrillating ventricles to auricles, but that the structures not participating in the delirium may contract as a whole and in a perfectly co-ordinate manner.

In the explanation of the fact that the fibrillary state is not transmitted through the auriculo-ventricular bundle, it might seem warrantable, in the absence of experimental data, to attribute it to special physiologic properties of the tissue composing the bundle, to the fact, for example, that contractility has not yet been demonstrated for Purkinje tissue unmixed with muscle cells.[2] On the other hand it is possible that the narrowness of this conducting isthmus may suffice to account for its relation to the spread of the fibrillary process.

[1] Vulpian: Archives de physiologie, 1874, p. 976. W. T. Porter: This journal, 1898, i, pp. 77–81. Erlanger and Hirschfelder: This journal, 1906, xv, p. 167. Cushney and Edmunds: American journal of medical sciences, 1907, cxxxiii, p. 74 *et seq.* W. E. Garrey: This journal, 1908, xxi, p. 287.

[2] J. Erlanger: This journal, 1912, xxx, p. 405.

That the latter view is the probable one is indicated by the behavior of narrow strips as described in the previous section; that it is the correct one was easily proven by direct experiments in which only a narrow isthmus of muscle was left between portions of the auricles in order to determine whether fibrillation could pass from one side to the other. The following abbreviated protocols give the results of the experiments.[1]

Dec. 16, 1912. — The heart of an etherized cat was removed and perfused through the aorta and coronary arteries with Locke's solution (without glucose or oxygen). A cut was made between the auricles in the anterior part of the vault to the left of the septum. This cut was extended until a distinct delay in the passage of impulses from the right to the left auricle was noticed, then very carefully extended until a permanent partial block for normal impulses was induced. Faradization of the right auricle produced fibrillation which continued for a short time after faradization was stopped. The fibrillation did not involve the left auricle, which beat co-ordinately but irregularly. In similar manner fibrillation of the left auricle, which lasted only during the period of stimulation, did not extend to the right auricle across the connecting isthmus of muscular tissue. Owing to the ready recovery of co-ordinated contractions in these auricles the same experimental results were repeatedly obtained.

Dec. 18, 1912. — Artificial respiration was established on a large etherized cat. The heart was exposed by cutting away the anterior chest wall. With heavy-jawed haemostatic forceps the auricular tissue, at the left of the pulmonary veins, was crushed in a line so directed that a little more than the left appendix was separated from the auricles except for a narrow isthmus of normal muscular tissue, in which there was evident delay in the passage of impulses from the right to the left appendix. Fibrillation of the right auricle outlasted the causative faradization for a short time, but the left appendix continued to beat co-ordinately, although irregularly. Fibrillation of the (smaller) left appendix ceased when the causative faradization was stopped. During fibrillation of the left appendix, the right side of the auricles beat co-ordinately but irregularly.

[1] I am indebted to Dr. J. Erlanger for helpful co-operation in the performance of these experiments.

It is obvious from these experiments that a narrow bridge of normal auricular tissue behaved, so far as conduction of fibrillation was concerned, just as does the narrow auriculo-ventricular bundle.

The author extended these observations to the ventricular musculature of the dog, where permanent fibrillation is the rule. It was found that a sufficiently narrow bridge of tissue (a strip somewhat less than a centimetre wide was usually found to be sufficiently narrow) [1] left connecting the basal and apical halves can conduct normal impulses but will prevent the extension of fibrillation from one piece to the other, although individual impulses do pass and produce, at irregular intervals, contractions of the apical piece when the basal portion of the ventricles is fibrillating, or extra-systoles in the basal portion when the apical portion is fibrillating. In two of the experiments the ventricles were divided into two approximately equal masses, an apical and a basal portion, connected only by the moderator band. The results with this natural isthmus of normal muscular tissue were the same as those quoted above and need not be described in detail.

These experiments prove conclusively that it is impossible for the fibrillary state to be transmitted across a sufficiently narrow conducting bridge to non-fibrillating muscle; they offer the most obvious explanation of the fact that in the mammalian heart fibrillation does not extend through the His bundle, either from the auricles to ventricles, or in the reverse direction. It is not necessary to refer this property to any specialization or differentiation of the tissue or to any anatomic peculiarity other than the narrowness of the conducting bridge.

[1] The degree of narrowing necessary to prevent the extension of fibrillation will, naturally, vary with the physiological condition of the muscle. It would seem probable that the more irritable the tissue, the narrower the bridge must be; thus it was found by Porter (This journal, 1899, ii, p. 132) that fibrillation did extend across a very small muscular bridge, but that in other hearts it did not, "probably because the power of conduction in the bridge was too much reduced." Our clamping experiments show conclusively that the extension of the fibrillary process may be prevented in a bridge of any width when the conductivity is decreased by compression, although it is possible in such cases to still have some of the impulses pass the region of block and produce co-ordinate contractions.

III. Experiments with the Hearts of Turtles

The hearts of cold blooded animals are subject to inco-ordinated contractions which have been referred to in various terms, such as "undulatory movements" (Gaskell), "inter-vernucular action" (Mills), and by German writers as "Wogen und Wühlen." Bätke [1] has concluded, and we agree with him, that these are all true fibrillary contractions. We have repeated the procedures, which have been described above, in our work with mammalian hearts upon the hearts of large Pseudemys elegans. In the winter state of these hearts the inco-ordinated contractions of both auricles and ventricles are easily induced by faradization or by repeated or long continued vago-sympathetic stimulation, especially after the administration of atropine. It would be a needless repetition to detail the experiments; suffice it to say that in the recovery of the heart when subdivided, and in the relation of narrow strips and bridges of tissue toward conduction of the inco-ordination, the behavior of such hearts was identical with that of fibrillating mammalian cardiac tissue — an indication that the cardiac inco-ordinations are indeed true fibrillations.

What appears to be a striking example of the fact that large masses of tissue fibrillate more easily and recover less readily from the fibrillary state, is seen in the behavior of the ventricles of the large marine loggerhead turtle. Mills [2] noted the tendency of these hearts to fibrillate, and our experience indicates that it is indeed difficult to manipulate them in situ, or to remove them from the animals without precipitating the fibrillary contractions of the ventricles, although the auricles continue beating co-ordinately. Recovery from fibrillation may take place spontaneously, but not invariably, and the fibrillary process usually persists for a long time. When such ventricles are cut into centimetre cubes, these bits stop fibrillating, although they frequently contract rhythmically in the blood serum for several minutes before coming to rest. When stimulated by a few mechanical stimuli or faradically they contract rhythmically again but do not fibrillate. The

[1] H. Bätke: Archiv für die gesammte Physiologie, 1898, lxxi, p. 412; also *cf.* Langendorf: Archiv für die gesammte Physiologie, 1895, lxi, p. 314.

[2] T. W. Mills: Journal of anatomy and physiology, 1887, xxi, p. 1.

greater excitability and rhythmicity of these hearts may be in part responsible for the fibrillary tendency, but this factor only accentuates the importance of the mass factor. The large size, slow conductivity, and relative independence of vascular nutrition, as compared with the mammalian heart, coupled with the pronounced tendency to fibrillate, made it feasible to conduct upon the ventricles of marine turtles some experiments which have a fundamental bearing on the nature of the fibrillary contractions.

The Ring Experiment.—It was found that rings, two centimetres broad, cut from the base of the fibrillating ventricles of large loggerhead turtles did not recover from the fibrillary contractions. A most striking phenomenon resulted when such broad fibrillating rings were narrowed by incising midway between the outer and inner margins, the incisions in these cases not being carried completely around the ring. In this way, by separation of the inner and outer portions, a figure 8 was formed, the two loops being connected by the broad fibrillating isthmus; a second cut across this mass connecting the inner margins of the two loops converted the tissue into a single large ring one centimetre broad and from six to ten centimetres in diameter. As soon as this narrowing was completed it was found that the inco-ordinated fibrillary contractions had resolved themselves into a number of contraction waves which followed each other successively and repeatedly around and around the ring, all progressing in the same direction, an exhibition to which we may apply the term "circus contractions."[1] It usually so happened that the number of contraction waves gradually decreased until but a single contraction wave was left repeating its circuit again and again. In one instance such a wave continued around the ring for seven hours, making each circuit in from six to seven seconds, the diameter of the ring being ten centimetres. When such waves died out new ones were easily started by single mechanical stimuli. Faradic

[1] These experiments were conducted and publicly demonstrated at Woods Hole, Mass., before the appearance of the paper of R. G. Mines (Journal of physiology, 1913, xlvi, p. 349). Our rings were, however, cut from fibrillating tissue, which makes the results especially significant for the interpretation of the nature of the fibrillary process. Our conclusions are, in many respects similar to those of Mines (*l. c.*, p. 373).

stimuli did not cause fibrillation, but started a succession of waves, the number and distance between them being dependent upon the rate of progression and the duration of the refractory phases.

Experiments of this nature prove conclusively that fibrillary contractions are in reality normal in character when progressing along a narrow path, and that the abnormality is dependent upon the presence and relative complexity of the bypaths available. Romanes [1] studied the passage of impulses in rings of contractile tissue cut from the umbrella of the cover eyed medusa (Aurelia), and his studies have been extended by Mayer [2] working with the jelly fish (Cassiopea xamachana). The latter investigator has shown that by properly grading the compression applied to a ring near the point of stimulation, it is possible to block the progress of the contraction wave passing in one direction from the point stimulated, and by release at the proper moment to allow the wave which took the opposite course to continue its progress about the ring. By repeating the manoeuvre a number of waves, all making the circuits in the same direction, were started by what may be called the method of block.

Now the presence of blocks is exactly what we noticed in our ring preparations of the turtles' ventricles. The blocks, however, had developed spontaneously and affected the contraction waves passing in one direction only; those moving in the opposite direction passed the region of block and continued their progress about the ring. It was thus possible by simply touching the tissue at a point near the region of block to add a new wave to those already present.

The causes underlying the unidirectional selection by such blocks is not altogether clear, but appeared to be related to the irregular width of the strips on either side of the points of blocking, and consequently to differences in strengths of the impulses passing a given point of block. Be this as it may, the fact remains that spontaneous blocks of this type do appear, and, in our opinion, this fact is of greatest importance for any adequate theory of fibrillation. Furthermore, the close examination of these ring

[1] G. J. Romanes: Jelly fish, star fish and sea urchins, 1885, p. 67.

[2] A. G. Mayer: Popular science monthly, December, 1908, p. 481.

preparations revealed the equally important fact that *shifting* points of block are easily distinguishable. If, for example, a given area of the ring be closely watched each time the contraction passes it, it will often be found that at one time, only the tissue of the outer edge contracts and transmits the wave, while the inner edge remains quiescent. The next wave, however, may involve the inner margin, but the outer may not contract; or upon another circuit closest scrutiny reveals no superficial evidence of contraction, yet a wave of contraction may be seen to emerge again beyond the quiescent region and to proceed as if no obstruction had been offered to its progress; in reality none had been offered — the contracting elements were simply obscured by others which did not contract. In the very next circuit this same region may contract with all the appearances of normality. We possess in these observations the visible record of one of the fundamental phenomena of block which apparently are the cause of fibrillation.

IV. The Nature of the Fibrillary Process

For a complete refutation of the idea that fibrillation is due to the destruction of a co-ordinating centre (Kronecker), the work of McWilliam and of Porter has been conclusive. Our experiments amplify the proofs they have adduced.

That in the fibrillary process there is altered conductivity was clearly stated by McWilliam in 1887 (*loc. cit.*). We believe, however, that experiment does not confirm the view that the fibrillary process is sustained by new impulse formation in tissue of heightened excitability, a belief which also includes the more recent statement of this view by Lewis, who looks upon fibrillation as the result of extra-systole formation. Fibrillation of cardiac tissue may be induced by a sharply localized faradization, and while it is certainly true that the result of such stimulation is to raise the excitability with the possibility of extra-systole formation, our experiments have shown conclusively, however surprising the result may be, that the fibrillary process is not sustained by impulses arising in the portion of the tissue directly stimulated, for these portions may be removed without stopping the inco-

ordination, and once started, fibrillation may continue for a long time in tissue remote and physiologically isolated from the point stimulated.

Concerning the probable nature of the fibrillary process, Porter in 1894 made the following statement: "Fibrillar contractions of the heart may be due to an interruption of the contraction wave. The contraction wave would thus be prevented from running its usual course, and the normal co-ordinated action of the ventricular cells would give place to the confusion conspicuous in fibrillary contractions."

The results of our investigation are in complete harmony with and add substantial support to this block hypothesis. The experiments which we have described above brought out the fact that fibrillation could not persist in small pieces, which, however, were still large enough to be the seat of blocks. In explanation of this fact and of the fact that larger masses do fibrillate persistently, the following conception seems to be adequately supported by experimental data.

Normally the impulse to contract does not spread throughout the whole musculature from fibre to fibre, but is delivered simultaneously to many different parts of the musculature of the ventricle from the auriculo-ventricular conducting system. The probability of this condition was pointed out by Tawara [1] and the electrocardiographic studies of Erfmann [2] indicate the correctness of the surmise. The musculature of the ventricles thus beats apparently as a unit but in reality as a group of isolated segments each of which receives its impulse from a different branch of the conducting system. When, however, the stimuli are applied to the musculature directly, as in the induction of fibrillation, the transmission is from muscle fibre to muscle fibre and a distinct time interval elapses between the contractions of different portions of the structure. (This has also been shown to be the case by Erfmann, (*loc. cit.*). From the point stimulated the impulses can spread in any and all directions, their progress being limited only by the pre-existence or development of localized blocks within the tissue mass. Such blocks divert the impulse into other and

[1] S. Tawara: Das Reizleitungssystem des Säugethierherzens, 1906, p. 187.

[2] Wilh. Erfmann: Zeitschrift für Biologie, 1913, lxi, pp. 155–182.

more circuitous paths and the area so blocked off can participate in contraction only when an impulse which has passed to other portions of the ventricle approaches it from another direction; this area thus in turn becomes the centre from which the progress of contraction is continued, to be in its turn diverted by other blocks. The existence of such blocks, and especially of blocks of transitory character and shifting location, has been noted in the experiments detailed above. These conditions make possible the propagation of the contraction wave in a series of ringlike circuits of shifting locations and multiply complexity. It is in these " circus contractions " determined by the presence of blocks, that we see the essential phenomena of fibrillation.

In small masses of tissue blocks may exist, but the time necessary for the impulse to traverse all available circuits is within the refractory period and the mass contracts as a unit and fibrillation is thus impossible. In larger masses this is not true, for the larger the mass the greater the possible number and length of the circuits, and the greater the probability that each impulse will circulate until it reaches tissue which has once contracted but has passed out of the refractory state; thus a continuous circulation of impulses is inaugurated, which is fibrillation. Such a mechanism would account for the greater liability of large hearts to fibrillate and for the greater persistence of the fibrillary state in large tissue masses.

It is conceivable that the establishment of relative differences in excitability and conductivity in different parts of the musculature without the condition of absolute block might result in the same phenomena of "circus contractions" and fibrillation. Thus inequalities in temperature or unequal action of such drugs as digitalis or barium salts may precipitate fibrillation in some such manner, although we venture the suggestion that the action of the latter in inducing this state of inco-ordination will be found to lie in their well-known tendency to produce blocks. There is evidence at hand which indicates that this view of fibrillation is in complete harmony with the effects produced upon the fibrillary state by vagus stimulation.

Summary

The persistence of cardiac fibrillation is, other conditions being equal, directly proportional to the size of the tissue masses involved whether the pieces are cut from hearts already fibrillating or are faradically stimulated to start the process in them. The form of the tissue is important; for long narrow or thin pieces recover promptly, and narrow strips when connected with a fibrillating mass or when faradically stimulated do not fibrillate, but beat co-ordinately. Tissue rings cut from fibrillating hearts of marine turtles ceased fibrillating, but the contraction waves continued, repeating the circuit about the ring in co-ordinate "circus contractions." Sufficiently narrow bridges of any portion of the musculature of auricles or ventricles will prevent the extension of the fibrillary process and act thus like the auriculo-ventricular conducting bundle. When fibrillation is induced by localized faradization this locus may be subsequently excised, its inco-ordination will cease, just as will that of any other piece of similar size, while that of the remaining (larger) mass will continue, showing that the process, therefore, involves the whole tissue mass and is not sustained by impulses arising in any definite location.

The experiments support the block hypothesis and suggest that the blocks probably result in intramuscular ringlike circuits with resulting "circus contractions" which are fundamentally essential to the fibrillary process. Such ring circuits can exist in large masses but not in sufficiently small ones.

VARIATIONS IN THE SENSORY THRESHOLD FOR FARADIC STIMULATION IN NORMAL HUMAN SUBJECTS

II. The Nocturnal Variation

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IN the first communication of this series[1] a rhythmic variation in electro-cutaneous sensibility between the hours of 8.30 A.M. and 8.30 P.M. was described, and was shown to agree with variations in ergographic fatigue and in reaction time over the same period. Because there is this agreement among these quite dissimilar manifestations of nervous activity, the conclusion was drawn that they all depend upon the condition of the nervous mechanism as a whole. In other words, the variations in sensory threshold are of central rather than peripheral origin, and the threshold itself is a useful criterion of the condition of the nervous system. The present paper is an extension of the observations to cover the period between 8.30 P.M. and 8.30 A.M.

Method. — The sensory threshold was determined according to the method of Martin, Porter, and Nice,[2] in which liquid (saline) electrodes are used and the threshold stimulus is measured in β units.[3] The β units are obtained by computation from the Z units of Martin (*loc. cit.*). The latter are found by observation, in a properly calibrated inductorium, of the position of the secondary coil at which threshold stimulation is obtained when a current of known amperage is broken in the primary circuit. For calculating β several values of Z must be determined with different, known resistances in the secondary circuit. The

[1] Grabfield and Martin: This journal, 1913, xxxi, p. 300.

[2] Martin, Porter, and Nice: Psychological review, 1913, xx, p. 201.

[3] Martin: The measurement of induction shocks, New York, 1912, p. 76. See also Grabfield and Martin: *loc. cit.*, p. 301.

electrical resistance of the tissue undergoing stimulation must also be determined.

One of us (Wilbur) has worked out a useful simplification of the computation for β, which is as follows: The original equations of Martin are $\beta = \frac{ZA}{R+A}$ and $A = \frac{Z_r R' - Z_r R}{Z_{r'} - Z_r}$ in which R is the resistance of the secondary circuit when it includes only the secondary coil and the stimulated tissue, and R' the resistance of the same circuit after the inclusion of a known additional resistance; and Z_r and $Z_{r'}$ are the values of Z at resistances R and R' respectively. At least three values of Z_r for three different added resistances are always determined. If the expression for A is substituted for A in the equation for β above, and the resulting expression simplified, we have:

$$\beta = \frac{Z_r R' - Z_{r'} R}{R' - R}.$$

By adopting the expedient of using for the additional known resistances round numbers exclusively, as 10,000, 20,000, and 30,000 ohms, the denominator of the above expression becomes very simple and the solution of the entire equation not at all laborious. We have found the engineer's slide rule an indispensable aid in carrying out our numerous computations.

Observations. — Our conclusions are based on five series of observations on three different subjects. For one of these series we are indebted to Mr. Grabfield, who has kindly allowed us to incorporate with our own results an experiment carried out by him during the course of the study which was reported as the first paper of this series.[1] We should not feel justified in reporting so small a number of experiments were not the results rather unexpectedly concordant and reasonably in harmony with prevailing views as to the nocturnal state of the human nervous mechanism.

The experiments were carried out on the nights of July 13–14, 1912; July 9–10, 1913; and September 6–7, 1913. They could not well be made to conform to precisely similar conditions, therefore a brief description of each experiment is here given.

[1] Grabfield and Martin: *loc. cit.*

The experiment of July 13–14, 1912, had as subject a medical student, Bk, a young adult in good health. His sensory threshold was determined hourly from 4.30 P.M. During the intervals between stimulations he smoked cigarettes, read reclining, occasionally walked about. His evening meal was taken at 7.00 P.M. At 10.50 he went to bed, but did not sleep until after a threshold determination at 11.30. Between 11.30 and 6.30 the following morning the subject slept quite continuously, except during the taking of readings. When the time for a reading arrived he was wakened, bathed his head and hands in cold water, and the determinations were made as promptly as possible. The period of wakefulness did not exceed fifteen minutes in any case. Readings were taken at 12.30 P.M. and then at two-hourly intervals until 8.30 A.M.

In the experiments of July 9–10 and September 6–7, 1913, Bg. and W., healthy young medical students, acted alternately as subjects and observers. In the experiment of July 9–10 Bg. remained awake throughout the night. He occupied the intervals between determinations in computing the results of previous determinations and in reading. He smoked cigarettes occasionally. Subject W. was awake until midnight and slept during the intervals between determinations from that time till morning. He smoked two cigarettes early in the evening and one after waking in the morning. Threshold determinations were made hourly throughout this night. The procedure was as follows: At the proper time W. was wakened and went immediately to the room in which were the stimulating electrodes. His thresholds and tissue resistance were determined by Bg. as swiftly as possible; they were usually completed within five minutes from the time of waking. He then was replaced by Bg. whose thresholds were determined in like manner, W. acting as operator. At once after completing this second series of readings W. returned to his bed and fell asleep promptly. The entire waking period did not much exceed ten minutes.

On the night of September 6–7 both subjects slept between midnight and morning, being awakened at two-hourly intervals for threshold determinations by means of an alarm clock. The procedure was similar to that of the preceding experiment in that

W. acted each time as subject immediately after wakening and then made readings upon Bg. Both subjects went promptly to sleep after the determinations were completed.

Results. — The data obtained from the five experiments are given in Table I. Under each experiment the actual thresholds in β units are given in the first column, and the values of reciprocal $\beta \times 10^4$, adopted by Grabfield and Martin [1] as indices of irritability, in the second column. By examination of the figures representing irritability in the second column of each experiment the facts appear upon which this report is based. There was in general a decline in irritability during the evening from an early high point noted by Grabfield and Martin (*loc. cit.* p. 307) and confirmed by our observations. In each of the experiments there was a point of low irritability between 11.30 P.M. and 1.00 A.M., followed by some degree of recovery; and in four of the five experiments there was a second low point between 4.00 and 5.00 in the morning.

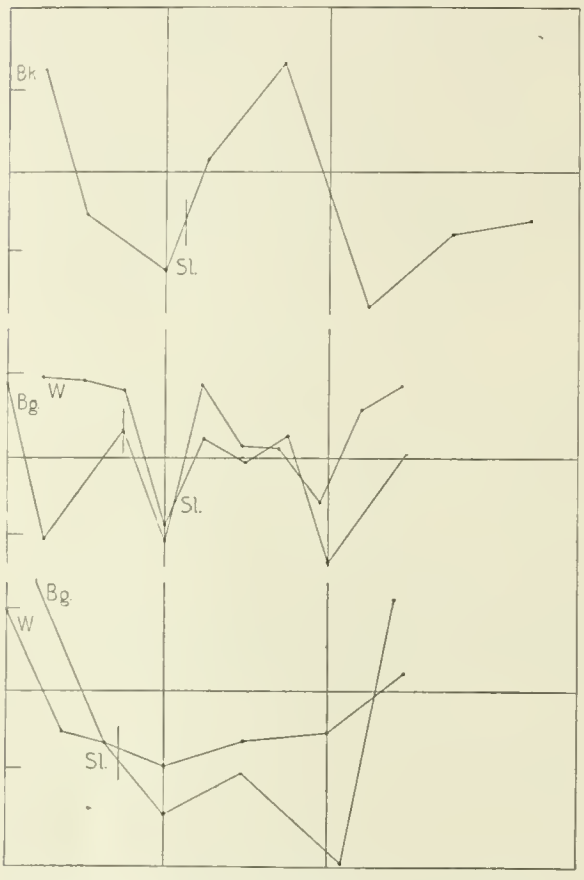


FIGURE 1. Nocturnal variations of irritability. No. 1, experiment of July 13–14, 1912. No. 2, experiment of July 9–10, 1913. No. 3, experiment of September 6–7, 1913. Individual irritabilities are represented in terms of percentage variations from average irritability. The extended abscissae are drawn at the level of average irritability. The extended ordinates indicate an interval of four hours. A short ordinate on each curve indicates midnight. The onset of the first sleep of the night is indicated by *Sl.*

To make the variations in irritability in the different experiments readily comparable the curves shown in Fig. 1 have been plotted. These are curves of irritability (reciprocal $\beta \times 10^4$) reduced to a percentage basis. In each experiment the average irritability for

[1] GRABFIELD and MARTIN: *loc. cit.*, p. 306.

TABLE I

Time P.M.	July 13–14, 1912		July 9–10, 1913				Sept. 6–7, 1913			
	Subject Bk.		Subject Bg.		Subject W.		Subject Bg.		Subject W.	
	β	recip β	β	recip β	β	recip β	β	recip β	β	recip β
7.30	61.9	161								
8.00			95.5	105	133	75	70.1	143	114.4	87
8.30	71.75	139								
9.00			73.5	136	126	79	58.3	171	121.6	82
9.30	85.6	117								
10.00			89	112	126	79				
10.30	88.8	112					77.8	129	143.5	70
11.00			81.8	122	127	79				
11.30	93.2	107					86.7	115	145.6	69
12.00	Sleep		77	130	151.6	66	Sleep		Sleep	
A.M. 12.30	79.5	126			Sleep					
1.00			89	112	134	75	97.1	103	150.9	66
1.30	Sleep				Sleep					
2.00			72.6	138	138	72	Sleep		Sleep	
2.30	71.3	140			Sleep					
3.00			78.5	127	133	75	91.4	109	145.6	69
3.30	Sleep				Sleep					
4.00			78.1	128	158	63	Sleep		Sleep	
4.30	97.7	102			Sleep					
5.00			83.9	119	148.5	67	104.4	96	143	70
5.30	Sleep				Sleep					
6.00			74.2	135	136.3	73			Sleep	
6.30	89.2	112								
7.00			72.5	138	145.7	68	68.5	146	133.7	75
7.30										
8.00										
8.30	86.6	115								

that experiment was drawn as a base line and the percentage variation from that average computed for each single irritability determination.[1] By plotting these latter data against the time intervals at which the determinations were made, the curves were constructed as shown.

Each experiment shows a point of low irritability near midnight. Exact coincidence in time of this point in different experiments is, of course, not to be expected. To our minds, however, the curves would be most instructive if the points of low irritability were superimposed. They were constructed, therefore, in that fashion. A short ordinate on each curve marks the position of midnight. The time at which the first sleep of the night began is indicated by the abbreviation Sl.

The time relation of the second point of low irritability to the first one is shown in a general way by an ordinate drawn to correspond with an interval of four hours from the first time of low irritability.

Significance of the Results. — We are not disposed to attempt to draw any far-reaching conclusions from the facts reported. So many factors undoubtedly are concerned in determining the condition of the nervous system at any time, that only after the accumulation of very numerous data will authoritative generalizations be justified. In one or two respects, however, our results seem to us significant. The two points of low irritability may perhaps be correlated with other well recognized physiological states occurring synchronously. Thus, the first low point corresponds in general with the period at which sleep ordinarily comes on, and may possibly be explained in terms of a raising of the nervous threshold accompanying the onset of the sleep taste. The second low point coincides fairly closely with the period of lowest body temperature, as determined by Jürgenson, Liebermeister, and others.[2]

Moreover, these points of low irritability are separated by about the same interval as was noted by Mönninghoff and Piesbergen[3]

[1] Grabfield and Martin: *loc. cit.*, p. 307.

[2] See Pembrey: Schäfer's textbook of physiology, Edinburgh and London, 1898, i, p. 799.

[3] Mönninghoff and Piesbergen: Zeitschrift für Biologie, 1883, xix, p. 114.

in their studies of the depth of sleep, as intervening between the periods of greatest sleep-intensity, and there is also a fair agreement in time between the periods of low irritability and those of great sleep-intensity. This coincidence may possibly signify that the rhythm which occurs in the human nervous system during the night is more or less independent of the state of sleeping or waking. Granting this as a valid possibility, the further assumption suggests itself, that the periods of deep sleep do not necessarily represent unusually great departures from the corresponding waking state, and need not therefore be exceptionally restful portions of the entire sleep interval. This assumption agrees with the common experience, voiced by Howell,[1] that short periods of deep sleep are not as effectual in restoring the nervous system as are longer periods of lighter sleep.

The experiment of July 9–10, 1913, (No. 2, Fig. 1), lends support to the suggestion that sleep, at least when interrupted at intervals as in this case, does not modify to any marked extent the state of the nervous system, judged by the sensory threshold. In this experiment one subject, W., slept during fully three-fourths of every hour from midnight to six in the morning. The other subject did not sleep at all. Yet the two curves are strikingly parallel. The parallelism of the curves is particularly interesting in view of the fact that the corresponding points are one hour apart.

A point to be emphasized in connection with the comparisons and suggestions made above is that our experiments did not include conditions which could be looked upon as representing extreme or even considerable fatigue. Our subjects had had no fatiguing experiences immediately previous to the experiments, nor were the experiments themselves specially wearying. Common experience shows that a single night of wakefulness after a day of ordinary activity may be endured without great discomfort and often without great desire for sleep. Our study had to do primarily with nocturnal variations of threshold in subjects as nearly normal as possible. The condition of the nervous system, both asleep and awake, during extreme fatigue, is a matter for further investigation.

[1] Howell: Textbook of physiology, 5th edition, Philadelphia, 1913, p. 255.

Summary

Experiments on young adult male human beings carried on during nights of wakefulness or of interrupted sleep show that the irritability of the nervous system, as indicated by the sensory threshold for faradic stimulation, sinks during the early part of the evening to a low point near midnight; recovers somewhat during succeeding hours; and sinks again about four hours after the first low point to a second low point. After this low point there is recovery of irritability to the daytime level.

. These variations in irritability are shown to correspond to variations in the depth of sleep as studied by Mönninghoff and Piesbergen. The suggestion is offered that both variations may be expressions of a deep-seated rhythm of the nervous system, more or less independent of the waking or sleeping state.

CONTRIBUTIONS TO THE PHYSIOLOGY OF THE STOMACH

XIII. THE VARIATIONS IN THE HUNGER CONTRACTIONS OF THE EMPTY STOMACH WITH AGE

By T. L. PATTERSON

[*From the Hull Physiological Laboratory of the University of Chicago and the Physiological Laboratory of the University of Maryland*]

THE experiments summarized in this report were undertaken at the suggestion of Professor Carlson to determine whether the activity of the empty stomach varies with the age of the animal. Some of Carlson's work on related problems seemed to indicate that the hunger contractions of the stomach decrease with the age of the animal, and the results of the following experiments confirm this idea. If the gastric hunger mechanism is closely correlated with the animal's actual need of food one would naturally think that the activity of a young animal's stomach would be much more marked than that of an aged animal, for healthy young animals are usually more active than older ones and this indicates a greater metabolic activity on the part of the organism, to say nothing of the additional requirements for growth. Apart from this correlation of gastric hunger activity with the food requirements of the animals at different ages, it is probable that the gastric hunger mechanism itself "grows old," parallel with the aging of the animal as a whole, as is the case with most of the organs of the body. As a rule, the increasing age of an organ is paralleled by decreasing activity of the organ. The stomach of an old animal may therefore exhibit less vigorous hunger contractions because of the actual age of the stomach itself, irrespective of correlations with bodily needs.

Method of Experimentation. — Four groups of dogs of different ages were selected; namely, a pup five to six months of age, a young adult, an adult, and an old adult. In all cases care was taken to choose only dogs in good condition and perfect health,

as far as could be judged by actions and external appearances. These dogs were operated on for gastric fistula according to the method described by Carlson[1] and as soon as the wound healed sufficiently, which usually required from five to seven days, the movements of the empty stomach were studied by Boldireff's method with the exception that a more delicate balloon was used which was connected with a chloroform manometer and used with a pressure of from three to six centimetres. The observations were made twenty-four hours after feeding, in order to assure an empty stomach. The animals were given at least one day or more of rest after each experiment so as to be in a perfectly normal condition when used again. During the taking of the records they were held in the lap, apparently without any appreciable discomfort for they nearly always slept through a large part of the experiment. In fact, they became so well trained after a few trials that when removed from the cages they would chase the experimenter from one room of the laboratory to another and watch for the first opportunity to jump into his lap in order to cuddle down and go to sleep. Five different series of records of the hunger movements of the empty stomach were obtained from each dog on five separate days, the continuous experimental periods ranging from two and a half to four and a half hours, respectively. This first series of dogs were then followed by a second similar series as controls.

In addition also to the two above series of dogs, a small pup five to six weeks of age was operated on for gastric fistula. This was on August 4, and three days later the wound had healed so that the first record of the stomach's movement was taken. This animal being so very small it was necessary of course to use a smaller balloon and also a different manometer. The balloon used was of the same delicacy as those used on the older dogs, but was only about one-third as large and connected with a water manometer with three to six centimetres' pressure. It was found impracticable to hold such a small animal in the lap so an armed office chair was selected and covered with a laboratory coat, the front of the chair seat being rather darkened and boxed in by raising the lower portion of the overlapping coat and attaching

[1] Carlson: This journal, 1913, xxxii, p. 369.

it. Here the pup was placed and after a trial or two he became so well accustomed to his new environment that nothing suited him better than a good long nap there. No control was run on this young pup because no other pup of that age was available, but of the series of records obtained several were of longer duration than any taken on the other dogs, the longest one representing a continuous period of six and one-half hours, in which there was only one true rest period lasting two and one-half minutes (Fig. 1). This particular record was commenced eighteen

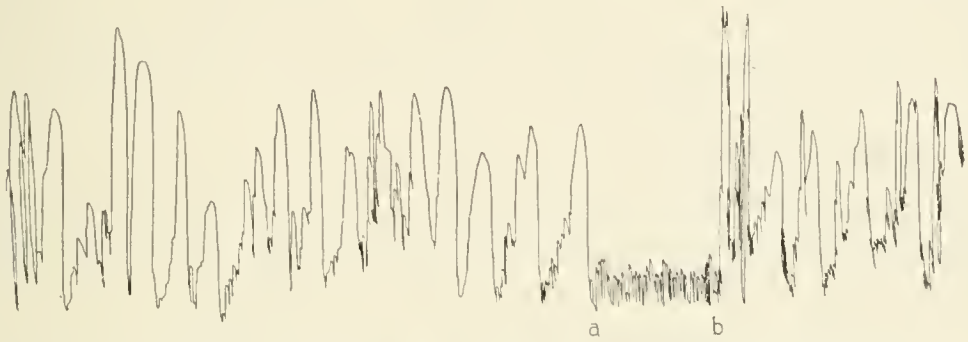


FIGURE 1. (One-half the original size.) Tracing from the empty stomach of a very young pup, five to six weeks of age, showing the very rapid contractions and the very short quiescence period, *a* to *b*, of two and one-half minutes' duration. Water manometer.

hours after the feeding of the animal. All the records were taken on a slowly moving drum revolving at the rate of about fifty minutes per revolution. The time for the contraction and quiescence periods was figured by means of a chronometer record.

RESULTS

The general character of the gastric hunger contractions in adult dogs has been reported by Carlson. After the introduction of the balloon into the stomach there is usually a short period of inhibition and then as the dog becomes quiet there is an increase in the tonus of the stomach. The strong hunger contractions gradually increase in amplitude and the pause between them becomes shorter and shorter until the period usually ends in very powerful and rapid contractions approaching incomplete tetanus. This is very evident in the older dogs and less so in the younger dogs, for the stronger contractions are going on practically all the time. Furthermore, the regularity of these movements is greatly

disturbed and also inhibited for a longer or shorter period depending on the disturbing influence, such as noise, fright, pain, anger, exciting influences, sight or smell of food, irritation such as around the fistula due to the presence of gastric juice, or by an unhealthy condition of the dog. In all the dogs studied the strong hunger contractions were usually preceded by restlessness as shown by the twitching of certain skeletal muscles, slight groaning, or stretching and waking from sleep, while sometimes these disturbances occurred in the upstroke of the curve, thus indicating that they are more or less disagreeable and painful to the animal. These effects appeared to be more magnified in the young animals than in the old, especially in the pups five to six weeks and five to six months of age, respectively.

The results summarized in Table I were computed from the tracings made from the different series of dogs and these figures in each case represent as nearly as possible the true time of activity and rest of the empty stomach, everything in the records of a doubtful character, or of an abnormal nature caused by disturbing influences, being entirely eliminated. The length of both the contraction and quiescence periods as observed by Boldireff seems on the whole to be considerably less than that shown in my series of old dogs (for doubtless he worked with old dogs). In fact, these two respective stomach periods seem to be much more variable in old dogs than in the young. My results on adult dogs are practically identical with those reported by Carlson. The differences between the results obtained by Boldireff and my own are probably due to the condition of the animals, the method of handling, and the method of registering the stomach contractions, for his dogs were forced by mechanical means to lie or stand in one position for six to twelve hours at a time, while mine were allowed to lie comfortably in the lap and sleep if they so desired. This forced position probably in part produced the brevity of the contraction periods. Boldireff's dogs also had other fistulae which would tend to make them more or less abnormal, perhaps interfering with the processes of digestion, while mine contained only the one fistula in the fundus portion of the stomach. A comparison of some of the records made from the different dogs may be had by a study of Figs. 1, 2, and 3.

TABLE I

SUMMARY OF OBSERVATIONS ON THE LENGTH OF THE CONTRACTION AND QUIESCENT PERIODS OF THE EMPTY STOMACH OF DOGS OF DIFFERENT AGES

First Series of Dogs				Controls		
Dogs	Sex	Length of contraction period	Length of quiescent period	Sex	Length of contraction period	Length of quiescent period
Old adult	♀	30 min. to 2 hr.	$1\frac{1}{6}$ to $3\frac{2}{3}$ hr.	♂	35 min. to $1\frac{3}{4}$ hr.	$1\frac{2}{3}$ to $4\frac{1}{6}$ hr.
Adult	♀	$1\frac{2}{3}$ to 3 hr.	$1\frac{1}{6}$ to 2 hr.	♀	$1\frac{1}{2}$ to 3 hr.	$1\frac{1}{2}$ to 2 hr.
Young adult	♀	$2\frac{3}{4}$ to $3\frac{3}{4}$ hr.	1 to $1_1^1{}_2$ hr.	♀	3 to $3\frac{3}{4}$ hr.	$1\frac{1}{4}$ to $1\frac{3}{4}$ hr.
Pup (age 5–6 mos.)	♂	3 to 4 hr.	5 to 10 min.	♀	3 to $4\frac{1}{3}$ hr.	5 to 10 min.
Young pup (age 5–6 wks.)	♂	$4\frac{1}{2}$ to $5\frac{2}{3}$ hr.	2.5 to 3.4 min.			

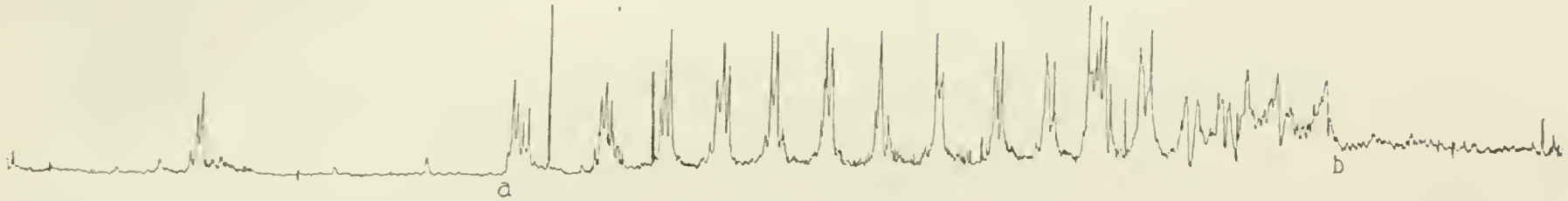


FIGURE 2. (One-third the original size.) Tracing from the empty stomach of an old dog showing a complete contraction period, *a* to *b*, of thirty minutes' duration. Chloroform manometer.

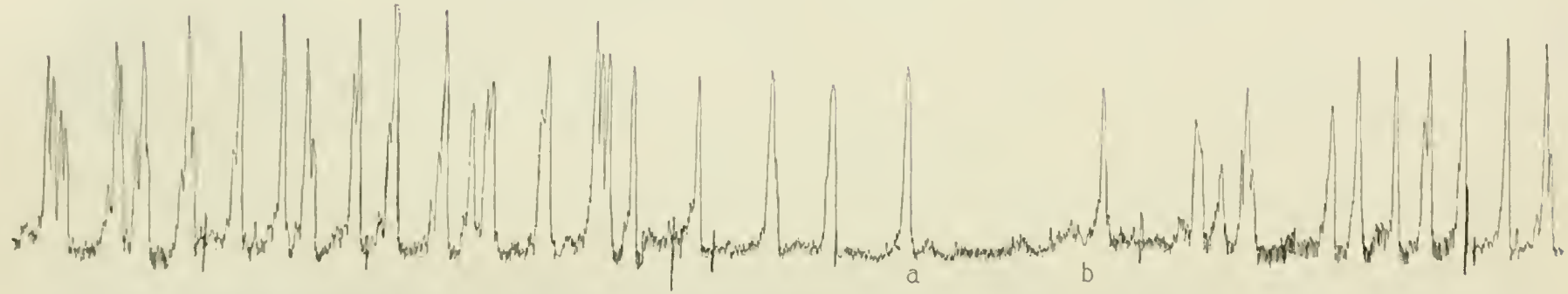


FIGURE 3. (One-third the original size.) Tracing from the empty stomach of a pup, five to six months of age, showing the short quiescence period, *a* to *b*, of six and twenty-five hundredths minutes' duration. Chloroform manometer.

As regards variation of stomach movements between dogs of different ages, the chief and practically the only constant difference was found in the length of the periods of contraction and the periods of quiescence. In all cases the periods of quiescence are the longest in old dogs, varying from one and one-sixth to four and one-sixth hours, and rapidly decreasing in length proportionately to age to two and one-half to three and four-tenths minutes in the very young pup of five to six weeks. Conversely the periods of contraction are the longest in the young dogs — for instance, in the very young pup the recorded periods run from four and one-half to five and two-thirds hours — and they rapidly decrease in length proportionately to age, in the old dogs from thirty minutes to two hours, thus showing that the stomach's activity is in direct proportion to the age of the animal.

The rapidity of the strong hunger contractions during the active periods appears on the whole to be greater in young animals than in old. The tonus of the stomach and also the strength of the contractions in young animals may be slightly higher, but they are subject to great variations. The decrease in the activity of the stomach as the animal approaches senility is probably an explanation in part at least for the more chronic gastric disturbances in the aged.

Summary

1. In healthy dogs the hunger contractions of the empty stomach decrease with age. This decrease appears to some extent in the tonus and in the rapidity of the hunger contractions, but is particularly marked in the duration of the periods of hunger activity and the intervening periods of quiescence of the stomach. On the whole the decrease in the gastric hunger activity is proportional to the advance in age. In very young dogs the hunger contractions of the empty stomach are practically continuous.

2. Two factors are probably involved in this variation of the gastric hunger contractions; namely: (1) the actual age of the gastric motor mechanism; (2) the correlation of the gastric hunger mechanism with the metabolic gradient or the need of food. The relative importance of these two factors must be determined by direct experiments.

AN EXPERIMENT TO PROVE THAT THE CILIA OF THE HUMAN NOSE WAFT TOWARD THE ANTERIOR NARES

By W. SOHIER BRYANT

THE author was so interested, from a clinical point of view, in the question of the direction in which the cilia of the nose waft that he conducted the following experiment: Fresh turbinal tissue from human turbinotomies was placed in isotonic saline solution at the body temperature and small pieces of rubber dam measuring 1. to 0.5 mm. were laid upon it. He observed that the rubber dam was moved *forward* with the adherent mucus at the rate of from one (1) to four (4) millimetres per hour.

This experiment was repeated on several occasions and conclusively proves what was theoretically anticipated, namely, that the cilia of the mucous membrane of the human nose waft toward the anterior nares and not toward the choanae.

From a theoretical point of view also, it would seem a priori that the cilia would cast the accumulated sediment from the inspired air out of the body in the most expeditious way, and the most expeditious way would be by the external nares. Also, the observation of collections of mucus containing dust and soot particles at the anterior nares suggests that the cilia waft in the direction of the anterior nares.

Especially noteworthy in this connection is the physiological convulsive explosion called "sneeze," a reflex act to clear the nose. The sneeze drives the contents of the nose from behind forward out of the anterior nares. If this explosion were against the direction of the cilia considerable traumatism would result to the delicate Schneiderian membrane.

In a careful search of the literature on this subject I was unable to find any statement that these cilia waft forward toward the anterior nares in man.

THE STATE OF THE VASOMOTOR CENTRE IN DIPHTHERIA INTOXICATION[1]

By W. T. PORTER and J. H. PRATT

[*From the Laboratory of Comparative Physiology in the Harvard Medical School.*]

Introduction

IN 1896 and 1899 Romberg and his students[2] published an influential experimental study on the nature of the circulatory disturbance in certain acute infectious diseases. They brought forward evidence which seemed to show that the collapse in experimental diphtheria and other infections which they produced in rabbits was due to paralysis of the vasomotor centre in the medulla oblongata. Subsequent investigators of this subject, Enriquez and Hallion,[3] Rolly,[4] von Stejskal,[5] Pässler and Rolly,[6] and Gottlieb,[7] accepted Romberg's conclusions, although Enriquez and Hallion, von Stejskal, and Gottlieb were of opinion that the heart also was directly injured.

In all these investigations, the opinion that the vasomotor centre is gravely affected or "paralyzed" is based upon the failure of the observer to obtain any rise in blood pressure in asphyxia, upon stimulation of the nasal mucous membrane, or on stimulation of the sciatic nerve. The testimony is entirely negative and is open to the objection inseparable from negative experimental results,

[1] Aided by a grant from the Proctor Fund for the study of chronic diseases.

[2] Pässler and Romberg: Verhandlungen des xiv Congresses für innere Medicin, Wiesbaden, 1896, p. 256. Romberg, Pässler, Bruhns, and Miller: Deutsches Archiv für klinische Medicin, 1899, lxiv, p. 652.

[3] Enriquez and Hallion: Archives de physiologie, 1898, p. 393.

[4] Rolly: Archiv für experimentelle Pathologie und Pharmakologie, 1899, xlii, p. 283.

[5] Von Stejskal: Zeitschrift für klinische Medicin, 1902, xliv, p. 367.

[6] Pässler and Rolly: Deutsches Archiv für klinische Medicin, 1903, lxxvii, p. 96.

[7] Gottlieb: Medizinische Klinik, 1905, i, p. 617.

namely, that the failure to obtain a reaction may be due to imperfections in technique.

We purpose in the present research to bring forward a positive, not a negative result.

Method

In this research diphtheria toxin was injected into an ear vein of rabbits. Some hours before death would probably have taken place, the state of the vasomotor centre was determined by measuring the reflex change in blood pressure obtained by stimulating the depressor and the sciatic nerves.

The results thus obtained were confirmed by measurements made upon an animal which had died from the disease and in which the circulation had been revived.

The details of the method are as follows.

The diphtheria toxin was obtained from the antitoxin and vaccine laboratory of the Massachusetts State Board of Health through Professor Theobald Smith and Mr. Herbert R. Brown, to whose courtesy we are much indebted. With the toxin first used, 0.005 c.c. was found to kill guinea pigs of 250 to 300 grams weight in 72 hours, with a variation of about 3 hours. To 2 c.c. of the toxin were added 8 c.c. normal saline solution (NaCl .008). Of this first dilution, 2 c.c. were further diluted by adding 198 c.c. normal saline solution. Thus 1 c.c. of the final mixture, called Solution II, contained .002 c.c. toxin. Of Solution II, one cubic centimetre per 500 grams of body weight was injected into an ear vein, usually the marginal vein. In a few experiments, a somewhat larger amount was used.

The question now arises whether the rabbits studied were gravely ill of the disease when the vasomotor reactions were measured. It would be expected that the hour of approaching death might be predicted (1) by the character of the symptoms and (2) by the time required for a measured quantity of toxin to kill an animal of given weight.

The symptoms unfortunately are of uncertain value. The rabbit refuses food and is apathetic, but there are frequently no further definite signs until just before death takes place. Even when the animal is no longer able to keep his erect posture or

hold up his head, but lies on his side, death may be postponed for several hours or it may occur in a few minutes. In short, prediction of the hour of death by observations of the symptoms is difficult and unsatisfactory.

There remains prediction based on the amount of toxin injected. Our observations on this subject are given in Table I.

TABLE I

THE NUMBER OF HOURS DURING WHICH RABBITS SURVIVED AFTER RECEIVING THE DIPHTHERIA TOXIN

Rabbit No.	Weight in grams	c.c. Toxin per kilo weight	Date of injection	Hours of life	Remarks
			1912		
14	1950	.006	12 m. Apr. 11	30 to 43	Died during night of Apr. 12.
16	2350	.006	1.20 p.m. Apr. 21	5 to 19	Found dead, Apr. 22, 9.30 A.M.
18	1950	.005	12.35 p.m. Apr. 23	6 to 18	Found dead on morning of Apr. 24
21	1500	.004	4.15 p.m. May 25	46	
			1914		
29	2150	.003	Jan. 13	31 to 36	The toxin employed on Nos. 29–42 was such that .0035 c.c. killed guinea pigs of 250 to 300 grams in 60 hours.
30	2025	.003	Jan. 13	55 to 63	
31	1700	.004	Jan. 13	34	
32	1500	.004	Jan. 13	46	
33	1000	.004	Jan. 13	40 to 46	
34	1300	.003	Jan. 15	94	
35	2000	.003	Jan. 15	56 to 57	
36	1750	.003	Jan. 15	92	
37	1350	.004	Jan. 18	41 to 44	
38	1550	.004	Jan. 18	41 to 42	
39	1400	.004	Jan. 18	50	
40	1550	.004	Jan. 18	37 to 38	
41	1400	.004	Jan. 18	29 to 30	
42	1400	.004	Jan. 18	34 to 35	

In this table the first four cases are those of rabbits in which death took place before the vasomotor reflexes could be measured. The remaining fourteen animals were injected for the purpose of determining how long rabbits would live after receiving toxin in amounts comparable to the amounts given the rabbits in which we measured the vasomotor reflexes. It appears that the first four animals in Table I died in 46 hours or less, while the average duration of life in the fourteen rabbits specially investigated was 50 hours.

In Table II are given data concerning the rabbits in which the vasomotor reflexes were measured. It will be noted that the measurements were begun as an average 39 hours after the injection of the toxin.

We have therefore the following premises. It is alleged that the vasomotor apparatus is deeply affected in fatal cases of diphtheria intoxication. Observations on fourteen rabbits show that death took place as an average in 50 hours. In ten other rabbits, similarly poisoned, the vasomotor reflexes were measured as an average 39 hours after injection. It seems reasonable to expect that at this time, 39 hours after injection and but 11 hours before probable death, the vasomotor apparatus would have been impaired, had its impairment been an important feature of the disease.

The Measurement of the Vasomotor Reflex. — It is known that curare and ether both affect the changes of blood pressure obtained by stimulating the afferent vasomotor nerves. Regarding curare, it is to be noted that a decisive number of our observations on the depressor nerve were made without this drug. The reflex from the sciatic nerve must of course be obtained from a curarized animal. In all such, the curare was injected in dilute solution slowly through the external jugular vein. The reflexes were measured through a period longer than that during which the curare might have caused a significant error in the readings.

The ether was given very cautiously, a few whiffs from time to time, in such a way as not to affect perceptibly the blood pressure during the observations.

Where artificial respiration was employed, the quantity of air used was the least that would keep the blood properly oxygenated.

Great care was used in the preparation and subsequent handling of the nerves. The stimulating current was from an inductorium supplied by constant Daniell cells and the current strength was that distinctly perceptible to the operator's tongue.

The mercury manometer was usually employed, but some blood pressures were recorded with a membrane manometer.

Blood Pressure at the Beginning of Stimulation.—Information regarding the state of the animal may be obtained from Table II,

TABLE II

Blood Pressure when Stimulation of Afferent Nerves was Begun

Rabbit No.	c.c. Toxin per kilo weight	Hours after inoculation	Blood pressure	Remarks
			mm. Hg	
4	.004	43	58	
6	.004	42	80	
7	.006	16 [1]	66	
8	.004	42	80	
9	.004	41	92	
10	.005	41	50	Low blood pressure probably due to curare and exposure of splanchnic nerves.
11	.004	41	46	Curare
12	.004	42	47	"
20	.004	39	97	"
21	.004	41	42	"

[1] This rabbit received an unusually large dose of toxin.

which shows the blood pressure at the time the stimulation of the afferent nerves was begun. The average blood pressure in the ten rabbits was 66 mm. Hg. In the five in which no curare was given, the blood pressure averaged 75 mm. Hg. It is clear that in these animals the blood pressure was not seriously affected. If it be urged that the blood pressure is seriously affected only in the very last hours of the disease, we present this additional observation upon a rabbit in which death was imminent.

Experiment January 19, 1914. — Rabbit No. 34, weighing 1300 grams, had received through the ear vein .003 c.c. diphtheria toxin at 5.10 P.M., January 15. On January 17, food was refused, but at 10 A.M., January 19, it was noted that the rabbit did not seem very ill. At 3 P.M., however, he was unable to stand, and at 3.30 he was flaccid and insensible and obviously near death. At that hour, the depressor nerve was exposed and a cannula placed in the carotid artery. The rabbit was wholly insensitive to the operation, so that no anaesthetic was necessary. The heart beats were so feeble that they scarcely lifted the lever of a sensitive membrane manometer, quite undamped. The blood pressure was 80 mm. Hg and fell to 50 mm. on stimulation of the depressor nerve, an absolute fall of 30 mm. (37.5 per cent). After stimulation, the blood pressure rose quickly to its former level.

Thus in our observations the blood pressure was not seriously lowered even in the last stages of the disease.[1]

The Depressor vs. the Sciatic Nerve as an Index to the State of the Vasomotor Cells. — The depressor nerve contains only afferent vasomotor fibres; the sciatic contains fibres of widely different functions. The depressor impulses reach the vasomotor centre directly; the sciatic impulses must pass first through the spinal cord, where the conducting apparatus is subject to influences not found in the case of the depressor nerve. The depressor reflex can be measured without administering a drug, whereas the sciatic reflex can be measured only after the administration of curare, a poison the effects of which cannot positively be limited to the motor end-plates. Finally, the depressor reflex can be measured without artificial respiration, but the sciatic reflex requires artificial respiration, the unskilful use of which introduces serious errors into measurements of blood pressure.

All these are excellent reasons for preferring the depressor nerve as the indicator of the condition of the bulbar vasomotor cells.

In this research the results gained with the depressor were confirmed by stimulation of the sciatic nerve.

[1] It is equally true that unless care and skill be employed, the blood pressure will fall rapidly under the operative procedure.

The Sciatic Vasomotor Reflex in Diphtheria Intoxication

For the reasons stated in the preceding paragraph we have used in this investigation chiefly the depressor nerve, but we have stimulated the sciatic nerve often enough to show that in diphtheria intoxication the sciatic reflex does not indicate a noteworthy change in the power of the vasomotor centre. The average rise from stimulation of the sciatic nerve was 33 per cent while the average fall from stimulation of the depressor nerve, as shall presently be shown, was 36 per cent. The observations on the sciatic reflex are given in Table III, showing 18 stimulations in 5 rabbits.

TABLE III

The Absolute and Percentile Change in Blood Pressure upon Stimulation of the Central End of the Sciatic Nerve at Different Levels

Beginning level of blood pressure	Number of observations	Average absolute rise	Average percentile rise
mm. Hg		mm. Hg	%
71 to 80	1	18	24
61 to 70	2	38	36
51 to 60	1	8	22
41 to 50	1	26	57
31 to 40	4	10	26
21 to 30	3	7	29
11 to 20	6	7	37

The Depressor Vasomotor Reflex in Diphtheria Intoxication

The measurements of the depressor reflex may be divided into two series. The first consists of 23 observations on ten rabbits, between March 29, 1912, and May 25, 1912. The second series contains the rabbits of January 19 and January 20, 1914.

First Series. — The observations of the first series appear in

Table IV. It is seen that in measurements made at initial blood pressures between 30 and 100 mm. Hg the average fall on stimu-

TABLE IV

THE ABSOLUTE AND THE PERCENTILE CHANGE IN BLOOD PRESSURE UPON STIMULATION OF THE CENTRAL END OF THE DEPRESSOR NERVE AT DIFFERENT LEVELS

Initial level of blood pressure	Number of observations	Average absolute fall	Average percentile fall
mm. Hg		mm. Hg	%
91 to 100	1	19	20
81 to 90	6	33	40
71 to 80	2	38	48
61 to 70	4	23	35
51 to 60	2	20	38
41 to 50	4	19	38
31 to 40	4	13	35

lation of the depressor nerve was 36 per cent*;[1] a fall as great or greater than that obtained in animals not poisoned with diphtheria toxin.[2]

The conclusion is inevitable that in rabbits examined as an average 39 hours after receiving a lethal dose and 11 hours before their probable death from diphtheria toxin the vasomotor centre is substantially normal.

It is highly probable that the vasomotor centre would at this time (39 hours after the lethal dose was administered) have been impaired were diphtheria toxin specifically injurious to the vasomotor cells.

Second Series. — Conclusive evidence against the hypothesis that the vasomotor centre is "paralyzed" in diphtheria intoxication is afforded by the experiments of January 19 and January 20. The

[1] In 262 observations on unpoisoned animals made by W. T. Porter the average depressor fall was 33 per cent.

[2] W. T. PORTER: This journal, 1907, xx, p. 403.

protocol of the first of these experiments, given on page 436, clearly indicates that the rabbit, "flaccid and insensible," was about to die. In the experiment of January 20, systemic death had actually taken place, the respiration had ceased beyond recall, the heart had stopped, the arteries were empty, but the vasomotor cells were still intact and the heart was made to beat again long enough for the vasomotor reflex to be measured. Following is the protocol.

Experiment January 20, 1914. — A rabbit weighing 1400 grams received in the ear vein .004 c.c. diphtheria toxin at 1.05 P.M, January 18. The morning of January 20 the rabbit seemed listless. It was placed on a table and observed continuously from 9 A.M. As the day wore on, the rabbit could not hold up the head, nor regain his feet when laid upon one side. Finally,

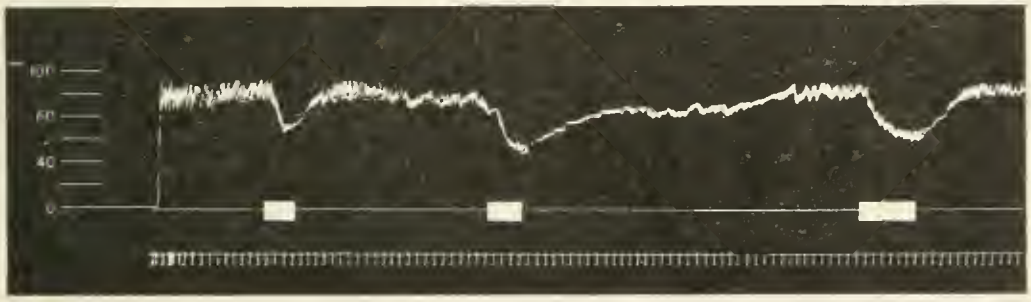


FIGURE 1. From an animal dead of diphtheria toxin, but with surviving vasomotor cells and resuscitated circulation. The upper line shows carotid blood pressure recorded with a membrane manometer. The graduation scale in mm. Hg is seen at the left. The middle line records the atmospheric pressure and the stimulation of the depressor nerve. The lower line gives time in 5-second intervals.

about 3.15 P.M., he lay prone, the head stretched on the table, and the respiration feeble and labored. At 3.30 he seemed so near death, that he was placed on the operating board. Death at once followed; there was no corneal reflex, no respiration, no heart beat, the carotid artery seemed empty, and the rectal temperature was 32° C. The rabbit was completely insensitive. It was quickly tracheotomized and artificial respiration was established. Warm normal saline solution was injected into the external jugular vein. The heart began to beat, though feebly, scarcely raising the writing point of a membrane manometer, completely undamped. The carotid pressure rose to about 80 mm. Hg. Both vagi were now cut and the depressor nerve was stimulated; three of the stimulations are shown in Fig. 1; in

these three the pressure fell on stimulation from 80, 70, and 72 mm. Hg to 52, 40, and 45 mm., respectively; an absolute fall of 28, 30, and 27 mm. Hg, and a percentile fall of 35, 43, and 38.

Thus, a normal reaction from the vasomotor centre was obtained on stimulating the depressor nerve in an animal that had died of diphtheria intoxication.

Conclusion

The experimental evidence proves that the vasomotor centre is not impaired in fatal diphtheria intoxication.

PROCEEDINGS OF THE AMERICAN PHYSIOLOGICAL SOCIETY

TWENTY-SIXTH ANNUAL MEETING

PHILADELPHIA, DECEMBER 29, 30, 31, 1913

PROCEEDINGS OF THE AMERICAN
PHYSIOLOGICAL SOCIETY

THE CONTOUR OF THE INTRAVENTRICULAR AND THE PULMONARY ARTERIAL PRESSURE CURVES BY TWO NEW OPTICALLY RECORDING MANOMETERS

By CARL J. WIGGERS

A study of the pressure variations in the right ventricle and the pulmonary artery was undertaken, not merely to establish the normal pressure curves, but also to determine what factors were capable of modifying their contour. In such an analysis it was hoped to find the key for interpreting and explaining the changes that the acts of respiration cause in the pulmonary and systemic blood pressures.

In order to study these changes with instruments combining a high vibration frequency and great sensitiveness with convenience in application and operation two new forms of optically recording manometers were shown, the details of which will be described in other communications to appear in this Journal.

Results: The pressure curve in the right ventricle obtained under normal conditions of venous and pulmonary arterial pressures may be divided into (*a*) an auricular period, (*b*) an isometric period, (*c*) an ejection period, and (*d*) a relaxation period. The steepness of the isometric curve (i.e., while the tricuspid and semilunar valves remain closed) is modified by (1) auricular pressures and (2) vigor of cardiac contraction. Its height, regulated by the diastolic arterial pressure previous to opening of the semilunars, is modified by (1) the auricular pressure and (2) changes in the resistance within the pulmonary circuit. Comparison

shows that the curves obtained after compressing the lung vessels modify the height of the isometric period in a manner directly opposite to lung inflation (natural or artificial). This leads to the inference, which is substantiated by the change in the pulmonary arterial pressure curve, that during lung inflation the pulmonary vessels are dilated.

The curve of the ejection period, which follows opening of the semilunar valves, corresponds in shape to the pressure curve within the pulmonary artery. It rises, reaches its summit, and then declines until the semilunar valves close. The rapidity of the rise and the lapse of time before the summit is reached determine whether the curve, as a whole, when written on a more slowly moving film, gives the appearance of a rounded or flattened top. Since this is determined by the pulmonary arterial pressure, it follows that the factors above mentioned may decidedly affect the contour of the pressure curve.

A negative extra cardial pressure, when great, decreases the steepness and height of the isometric contraction, both by impeding the diastole and diminishing the initial tension for ventricular contraction. So far no evidence has been obtained, however, that variations such as normally occur in the unopened chest affect the intraventricular pressure curve.

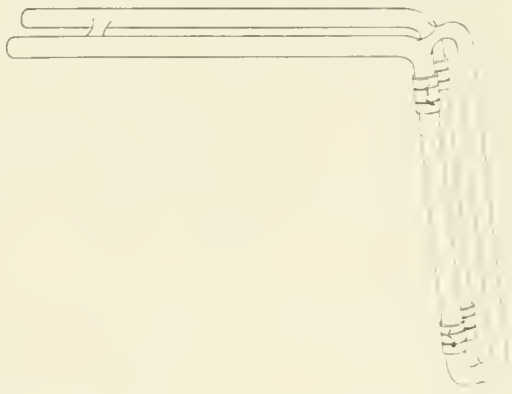
THE DIALYSIS OF THE NORMAL CIRCULATING BLOOD

By C. L. v. HESS and H. McGUIGAN

A simple method of dialyzing the normal circulating blood was devised primarily to determine the condition of the sugar in the blood. It was intended so far as possible to avoid the decomposition of the form elements and the possible breakdown of any sugar compound if such existed. Many other problems may be attacked by the method.

The method consists in attaching a dialyzing apparatus of artificial blood vessels composed of collodion, between the carotid artery and external jugular vein. A connection may be made

between any other artery and vein. No anticoagulant was used. Clotting in the dialyzer was prevented by flushing out the apparatus about every ten minutes. This is easily accomplished if three-way cannulas are used to connect the artery and vein with the dialyzer. The diagram shows the dialyzer.



The authors were unaware of the priority of Abel in this field. The method must be looked upon as a modification of his. The main difference is that we strenuously avoided the use of an anticoagulant while he used hirudin with great liberality. This allowed him to use a more complicated apparatus and a greatly increased dialyzing surface.

The method shows that most of the sugar, perhaps all, is in the free state. Phloridzin does not increase the rate of dialysis, even when the urine contains an abundance of sugar. In one trial diastase was found free in the dialyzate, though in this case we did not work aseptically. Hexamethylenamin is not decomposed in the circulating blood.

THE CONDITION OF THE BLOOD IN HEMOPHILIA

By W. H. HOWELL

The paper gave the results of the examination of the blood of two boys presenting a typical history of congenital hemophilia. The cases were examined repeatedly over a period of a year.

Coagulation Time. — The blood was taken by venepuncture and 2 c.c. were placed in clean weighing tubes to clot. As determined by this method the coagulation time of normal blood varied between twenty and forty minutes, that of the hemophilic blood between four and five hours.

Antithrombin. — The antithrombin was estimated in the clear plasma of the oxalated blood after heating to 60° C. to destroy the fibrinogen and prothrombin. The antithrombin value was estimated by determining the delay in clotting caused by this heated plasma when added to known mixtures of fibrinogen and thrombin. The results of fourteen examinations indicated that the antithrombin in hemophilic blood is present in amounts equal to, or, in some cases, slightly in excess of that shown by normal blood.

Prothrombin. — The tests used to determine this factor indicated that the available prothrombin in hemophilic blood is markedly less than in normal blood. The author concluded that the characteristic delay in coagulation in hemophilic blood is caused by this diminution in prothrombin. It was stated that the blood of dogs may be brought into a hemophilic condition, as defined above, by the injection of large doses of epinephrin.

FARADIC STIMULI: — A PHYSICAL AND PHYSIOLOGICAL STUDY

By JOSEPH ERLANGER and WALTER E. GARREY

The form and duration of induction shocks yielded by coils of the Du Bois-Reymond type, as determined by the string galvanometer and controlled by various physical and physiological means, while fairly constant for any one coil, vary considerably in the case of different coils. The stimulating value of the shocks is dependent entirely upon their ascending limbs and obeys the Du Bois-Reymond law. The decline of potential, even when it is made to take place instantaneously, does not seem to affect the stimulating value of the shocks. The duration of the shocks is much greater than the figures given in physiological literature, and this duration of the unmodified shocks may be greatly increased by foreshortening (short-circuiting) the shock. A make shock foreshortened to its crest may have a lower thresh-

old amplitude than the full break, and occasionally the threshold of the former, as determined by the position of the secondary coil, may be lower than that of the latter. Increasing the strength of the shocks increases perceptibly their duration, certainly in the phase beyond the crest. Strong shocks seem to be relatively more efficient physiologically than weak shocks.

When the rate of interruption of the primary is progressively increased the make and break shocks soon begin to overlap and to reduce mutually their amplitudes of potential, the break shock first being affected. Therefore, beyond a relatively slow rate of interruption, a rate that is determined primarily by the duration of the make shock, the threshold stimulating value of interrupted currents decreases as the rate increases. When at these rates the attempt is made to short-circuit out the make, the break shock is still further reduced in amplitude and the foreshortened make that always results may acquire a higher stimulating value than the break, and so reverse the stimulating pole.

A METHOD OF OBTAINING SUCCESSIVE CONTRAST OF THE SENSATIONS OF HUNGER AND APPETITE

By A. J. CARLSON

The experiment consists in swallowing a rubber balloon with rubber tubing attachment for recording the gastric hunger contractions, and a second rubber tube for the introduction of liquids or semisolids into the stomach without coming in contact with the mouth and the oesophagus.

At the height of a hunger contraction as shown by the recording manometer and by the intensity of the hunger sensation, cold water, beer, weak acids, or weak alcohol is introduced into the stomach by means of the second tube. These substances cause a temporary inhibition of the hunger contractions and hence abolish the hunger sensation; but the stimulation of the gastric mucosa by these substances gives rise to a sensation that appears to be identical with the sensation of appetite. When

the two sensations are compared by this device for placing them in successive contrast, they are plainly of different orders and not different degrees of the same kind of sensation.

The hunger sensation is essentially of an *unpleasant character* and when intense it is distinctly painful (protopatic pain). The appetite sensation induced by the stimulation of the normal gastric mucosa is essentially of a *pleasant character* and never under any circumstances painful.

A SUMMARY OF WORK ACCOMPLISHED WITH A RESPIRATION CALORIMETER IN BELLEVUE HOSPITAL

By EUGENE F. DuBOIS

The new respiration calorimeter of the Russell Sage Institute of Pathology resembles Benedict's bed calorimeter in Boston. Electric and alcohol checks have shown that the instrument can measure heat within 1.0%, oxygen within 0.34%, carbon dioxide within 0.28%, and water within 2.98%. The average respiratory quotient for alcohol has been 0.6670 instead of the theoretical quotient of 0.6667. In a total of 66 experiments on patients with various diseases the methods of direct and indirect calorimetry have agreed within 5% in two-thirds of the cases and within 3.5% in the total measurement of over 15,000 calories.

The average heat production of normal controls is 34.4 calories per hour per square metre of body surface. Working with Dr. Warren Coleman the metabolism of typhoid patients has been studied and it has been found that at the height of the fever the heat production is 30–50% above the normal average. At this stage of the disease meals containing 100 gr. of glucose or 10–11 gr. of nitrogen show little or no specific dynamic action although the same meals cause a rise of 10–15% in heat production in convalescence. It has been found also that the water elimination averages 33% higher in fever than in convalescence.

ON THE RAPID DISAPPEARANCE FROM THE BLOOD OF LARGE QUANTITIES OF DEXTROSE INJECTED INTRAVENOUSLY

By I. S. KLEINER and S. J. MELTZER

When large quantities of dextrose (4 gr. per kg. in a 20% solution) are introduced intravenously into dogs, the dextrose rapidly disappears from the blood. On an average 97% is lost from the blood in one and one-half hours. Of this, an average of 53% is found in the urine and 44% remains to be accounted for. With the kidneys ligated the amount of dextrose not accounted for is increased by about the amount which would have been in the urine if the renal function had been present, i.e., nearly all has disappeared from the blood. To exclude the liver and the other abdominal organs which may be concerned in decomposing or storing up sugar, in nine experiments the aorta and vena cava were tied near the diaphragm; in some cases also the thoracic duct was ligated and the thyroid glands removed. In the course of about an hour an average of about 84% had disappeared from the blood. It is therefore possible that the liver or some other abdominal organ is responsible for the disappearance of a small fraction of the dextrose in the experiments preceding this series.

In order to exclude the actual utilization of dextrose by the living tissues we next injected the sugar into dead animals. It was found that the dextrose leaves the blood quite rapidly, although not as quickly or as completely as in the living animal. In five experiments an average of 52.4% left the blood in a short time. Analysis of muscle tissue at the beginning and end of the experiment showed increases in carbohydrates calculated to be sufficient to account for the discrepancy. A similar result was obtained with dead animals having the aorta and vena cava tied.

In the muscle of the living animal there can also be found a large proportion of the dextrose lost from the blood, but sufficient work has not yet been done to determine whether any fraction undergoes decomposition or condensation.

Our general conclusion is that the disappearance of injected

dextrose is accomplished largely by passage into adjacent tissues, particularly the muscles. Physical factors alone are concerned in this process in the experiments on dead animals and it is quite probable that in the living animal vital factors play a less important rôle in this matter than has been ascribed to them by some investigators.

THE RELATIVE SYSTOLIC DISCHARGES OF THE RIGHT AND LEFT VENTRICLES AND THEIR BEARING ON PULMONARY DEPLETION AND CONGESTION

By Y. HENDERSON and A. L. PRINCE

In the excised cat's heart under coronary perfusion graphic records of the stroke of the right and left ventricles were obtained under various diastolic distending pressures.

The principal part of the apparatus connected with the heart consisted of two glass cylinders. In the lower end of each a brass cannula of suitable length and bore was held by means of a perforated rubber stopper. One of the cannulas was introduced into the left ventricle through one of the severed pulmonary veins, the other into the right ventricle through the superior vena cava. The closure of the mitral and tricuspid valves about the cannulas prevented regurgitation into the auricles. The diastolic distending pressure in either ventricle could be varied by the addition or removal of fluid in the cylinders. The oscillations of the fluid column in the cylinders, representing the ventricular stroke, was recorded by air transmission. The perfusion fluid consisted of equal parts of defibrinated sheep's blood and Locke's solution. The same mixture was used in the pressure chambers. All pressures mentioned subsequently refer to the diastolic distending pressure in millimetres of saline.

Three groups of experiments are presented. In the first, the right ventricular pressure was maintained at 50 mm. and that in the left was gradually raised from 0 to 210 mm; in the second the pressure was progressively and simultaneously increased in both ventricles from 0 to 170 mm.; and in the third the pressure

in the right ventricle was gradually increased, the left ventricular pressure remaining constant.

It was found that the right ventricle attains its maximum efficiency at 50 mm., pressures above 70 mm. causing a progressive decrease in the amplitude of its stroke. The stroke of the left ventricle at pressures below 50 mm. is always smaller than that of the right. Above 50 mm. the left ventricular output increases gradually, being equal to that of the right at 50 to 70 mm., and reaching its maximum at about 170 mm. With diastolic pressures of 50–70 mm. in both ventricles, the respective strokes are in equilibrium.

These observations serve as a basis for the conclusion that the pulmonary volume may be regulated in great part by the relative efficiency of the two ventricles. In life pulmonary depletion would be prevented by the inefficiency of the left ventricle at low diastolic distending pressures. Above 70 mm. the stroke of the left ventricle is always greater than that of the right at any pressure. Pulmonary congestion is thus normally prevented, as any increase in the pulmonary blood volume leads to a rise in left auricular pressure and thus induces an increased activity on the part of the left heart, by which the excess blood is pumped out of the lungs until pressure and volume are again normal.

THE EFFECT OF STRYCHNIN ON REFLEX THRESHOLDS

By E. L. PORTER

The experiments were performed on cats made spinal by cutting the cord in the neck and pithing the brain. A Sherrington electrode was placed on the tibial nerve and reflex movements elicited by single break shocks applied to its central end. At frequent intervals the thresholds of the flexion reflex, of the crossed-extension reflex, and of reflex extension of the fore-limb were determined by Martin's method.

Strychnin sulphate in 0.1 mg. doses was injected into the jugular vein at intervals of 2 to 10 minutes until the animal

exhibited violent convulsions. Before the injection the flexion threshold had usually a value of between 2 and 10 Z units. The crossed-extension threshold varied more widely, ranging from 5 to 300 Z units, and extension of the fore-limb could not be elicited by any strength of stimulus. In about one out of three animals after injection it was found impossible to demonstrate any lowering of the flexion threshold, although the thresholds for crossed-extension and for extension of the fore-limb dropped to within 2 Z units, or less, of the flexion threshold. In the remainder of the animals there was the same lowering of the thresholds for crossed-extension and extension of the fore-limb, and in addition a lowering of the flexion threshold of from 8 to 50 per cent.

THE ACCELERATION OF THE HEART IN EXERCISE

By H. S. GASSER and W. J. MEEK

A study was made of the parts played by the various mechanisms which have been described as producing an acceleration of the heart in the accelerations occurring in exercise. The experiments were done on dogs and the exercise consisted in running for two minutes. The reaction of the heart of the normal animal was compared with that occurring after one or more mechanisms had been removed.

After removal of the stellate ganglia no significant change was found in the actual acceleration in beats per minute. After vagotomy the acceleration was much impaired if two or three days were allowed to elapse for the accommodation of the respiration. After vagotomy and removal of the accelerators the findings were similar to those observed after vagotomy alone. If the extrinsic nerves of the heart were cut and the adrenals removed, neither exercise, asphyxia, nor anaesthesia produced any appreciable acceleration of the heart, although large accelerations were obtained before the extirpation of the adrenals. Acceleration is also possible over the accelerator innervation of the heart alone as it occurs after the vagi are cut and the adrenals removed. The

residual acceleration after adrenalectomy and cutting of the extrinsic cardiac nerves practically corresponds to that observed by Martin and others as occurring in the isolated mammalian heart for similar rises of temperature.

We conclude from our experiments that the acceleration of the heart in exercise is due mainly to inhibition of the cardio-inhibitory centre. This is aided especially in the more extreme conditions by the activity of the accelerator mechanism and the secretion of the adrenals. Temperature is a factor only as it affects the heart directly and does not depend on the stimulation of a reflex arc arising in and ending in the heart.

SOME MUTUAL RELATIONS OF OXALATES, SALTS OF MAGNESIUM AND CALCIUM; THEIR CONCURRENT AND ANTAGONISTIC ACTIONS

By F. L. GATES and S. J. MELTZER

At the October meeting of the Society for Experimental Biology and Medicine we reported our experiments on the combined action of sodium oxalate and magnesium sulphate on rabbits. We found that when a dose of 0.2 gm. of sodium oxalate is given subcutaneously on one side, and 0.8 gm. of magnesium sulphate is given on the other side, the animal sinks into deep anaesthesia and paralysis, equal to that produced by a dose of magnesium sulphate twice that given in the present instance. There is this difference, however, that the deep anaesthesia lasts a good deal longer than in the case of the double dose of magnesium alone. These experiments were undertaken on the basis of the well-known observations of Meltzer and Auer, that an injection of a calcium salt counteracts promptly a great part of the anaesthetic effect of magnesium, which seems to indicate that the normal conscious state depends upon the proper relation of magnesium to calcium in the fluids of the animal body. From this it would seem to follow that the same degree of anaesthesia could be produced either by an increase of magnesium or by a decrease of calcium. Since oxalates precipitate calcium we antic-

ipated that an injection of oxalate, with an inefficient dose of magnesium sulphate, would produce a deep anaesthesia equal to that from a much larger dose of magnesium sulphate alone.

Later we made observations upon the awakening effect of calcium in cases of deep anaesthesia produced by sodium oxalate plus magnesium sulphate. Intravenous injections of calcium chloride solutions are as strikingly efficient in these cases as in the deep states of anaesthesia produced by magnesium sulphate. In a minute or less after the beginning of the calcium injection the animal rouses, turns over, and sits up.

We have studied also the fatal effects of sodium oxalate given by intramuscular injection and the possibly favorable effect of the additional injection of magnesium sulphate or calcium chloride. Some of our results are as follows:

In 10 rabbits 0.2 gm. of sodium oxalate proved to be fatal in every case and the average duration of life was 30 minutes. All of the 10 rabbits which received 0.2 gm. of sodium oxalate intramuscularly, followed by one or more intravenous injections of calcium and sodium chloride, died, but the duration of life was 87 minutes. Of 10 rabbits which received 0.2 gm. of sodium oxalate and 0.4 gm. of magnesium sulphate, 4 remained alive, and the average duration of life in the six fatal cases was 137 minutes. Of 10 rabbits which received 0.2 gm. of sodium oxalate, 0.4 gm. of magnesium sulphate, and later 10 c.c. of a mixture of calcium and sodium chloride, 4 remained alive and the average duration of life in the six fatal cases amounted to 176 minutes.

THE OSMOTIC PROPERTIES OF CLAM'S MUSCLE

By E. B. MEIGS

The vitreous portion of the adductor muscle of the clam (*Venus mercenaria*) contains only 0.3% of chlorine, while the "clam-juice," by which the muscle is surrounded during the life of the animal, contains 1.6%. When the muscle is immersed for a day or more in sea water, double strength sea water, or 30% saccharose solution, the concentration of crystalloid in the muscle

rises to about half that of the surrounding solution, although the muscle remains alive throughout the period of its immersion. The muscle shows no tendency to lose weight in double strength sea water or 10% sodium chloride solution.

Experiments on the mantle, by which the adductor muscles are covered during the life of the clam, show that this tissue is nearly if not quite impermeable to sodium chloride.

There is, therefore, much reason to believe that the individual fibres of the clam's adductor muscle are not surrounded by semi-permeable membranes.

AN IMPROVED FORM OF APPARATUS FOR PERFUSION OF THE EXCISED MAMMALIAN HEART

By M. DRESBACH

The principal feature of the apparatus is a four-way stopcock which permits of the use of four different perfusion fluids in a single experiment, transition from one fluid to another being easily and quickly made without changing the pressure or temperature conditions under which the perfusion is being carried on. The stopcock is situated at the bottom of a cylindrical water bath, heated by a resistance coil and serving to bring the fluids to the desired temperature. A second bath raises the fluids to approximately the right temperature before they enter the main bath. The outlet of the stopcock, just below which the heart is suspended, contains a thermometer and connection for a manometer, which measure, at a point one inch above the aortic cannula, the temperature and pressure of the fluid being perfused. The capacity of the outlet tube is small; only one cubic centimetre of fluid must be displaced when one fluid is substituted for another. The side tube going to the manometer can be joined with a fifth fluid, which can be perfused at any desired temperature or pressure. The fluids are driven through the system by compressed air or oxygen. A fairly constant pressure can be obtained by making use of the principle of Hero's fountain.

The advantages of the apparatus are: simplicity of construc-

tion; convenience of operation; provision for use of at least five different solutions in one experiment; rapid and easy transition from one fluid to another; constancy of temperature and pressure.

SOME CHEMICAL FEATURES OF THE DIAPHRAGM AND OTHER SKELETAL MUSCLES

By FREDERIC S. LEE

In 1912 the author and Guenther reported the results of an investigation of certain of the physical features of the diaphragm of the cat as compared with certain other skeletal muscles. It was found that the diaphragm possesses a greater power of survival after the death of the animal, a greater resistance to the action of curare, a greater working power, a greater resistance to the oncoming of death, and a greater tendency toward rhythmicity in contraction. The investigation has now been continued with the aid of E. L. Scott, W. P. Colvin, and others into some of the chemical features of the muscles employed. These include the diaphragm as a muscle standing in some respects apart from all other skeletal muscles, the extensor longus digitorum and the sartorius as representatives of the paler muscles, and the soleus as a rèpresentative of the deeper red muscles. Thus far attention has been confined to the glycogen content, the power to reduce oxyhaemoglobin, and the phosphorus and sulphur contents of the lipoid fraction of the various muscles. The results are expressed in the following table in comparative figures, that of the diaphragm being reckoned in each case as a unit:

	Diaphragm	Extensor	Sartorius	Soleus
Glycogen	1.00	0.723	0.528	0.486
Reducing time	1.00	1.057	1.608	4.295
Lipoid phosphorus	1.00	1.015	1.440	
Lipoid sulphur	1.00	1.408	1.890	

It is seen from this table that with all four items the order of the muscles is the same; namely, the diaphragm, the extensor, the sartorius, the soleus. The greater content in glycogen which the diaphragm possesses may perhaps be associated with the greater working power of that muscle. The power to reduce oxyhaemoglobin was studied by means of Bonnhoffer's method. The muscles were quickly dissected out after death, rubbed up with powdered glass, placed at once in blood solution, and covered by a layer of olive oil to exclude the air. The time was then noted at which in each the spectrum of oxyhaemoglobin gave place to that of reduced haemoglobin. The diaphragm is seen to seize upon sufficient oxygen to bring about reduction somewhat more quickly than either of the pale muscles and much more quickly than the red soleus. The quantity of the phosphorus content of the lipoid fraction, which may perhaps be interpreted as signifying lecithin, is least in the diaphragm, slightly greater in the extensor, and still greater in the sartorius. The determination of lipoid phosphorus has not yet been made in the soleus. Similar quantitative relations exist with the sulphur content of the lipoid fraction, the significance of which is unknown.

THE EFFECT OF PULSATION ON FILTRATION

By R. A. GESELL

A method for filtering solutions under constant and pulsatile pressure was described.

Various solutions were filtered through various membranes, with and without stirring, and the rate and nature of the filtrate noted.

Without stirring, the rate of filtration during the periods of pulsatile pressure was greater than the rate during constant mean pressure. With stirring, the effect of pulsation on the rate of filtration was not as marked, but the enhancing effect of pulsation was noted.

With the methods employed for the detection of urea, sodium

chloride, albumin, and casein — pulsation apparently had no effect on the content of these substances in the filtrate. In three experiments, in which defibrinated blood was filtered through the dog's peritoneum, more globulin appeared in the filtrate during the periods of constant pressure than during the periods of pulsatile pressure.

THE RÔLE OF NASCENT OXYGEN IN PROTECTING THE BODY FROM SELF-DIGESTION

By W. E. BURGE

Ptyalin, rennin, pepsin, amylopsin, lipase, trypsin, and invertase are destroyed by nascent oxygen. The nascent oxygen was obtained by the decomposition of hydrogen peroxide by a piece of platinum gauze on which platinum black had been previously deposited by the passage of the current. The amount of nascent oxygen could be governed by the amount of hydrogen peroxide introduced into the enzyme solution in which the platinum gauze was immersed.

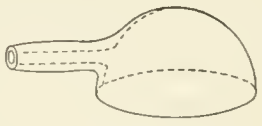
It was found that the amount of destruction of all these enzymes was more or less proportional to the amount of oxygen liberated in the solution and that all were destroyed by the amount of oxygen liberated from five cubic centimetres of hydrogen peroxide.

In the tissues, e.g., the stomach wall, there must be active or nascent oxygen because oxidation takes place there at a comparatively low temperature. From the above observations we know that pepsin is destroyed by nascent oxygen. A possible explanation of why the pepsin does not digest the stomach wall is that the active oxygen there oxidizes the pepsin which comes in contact with it. These observations also offer an explanation of why the diastatic enzymes in plants decrease during the day when nascent oxygen is being given off during the process of starch formation and why they increase in the dark when starch formation ceases.

CONVENIENT MODIFICATION FOR VENOUS PRESSURE DETERMINATIONS IN MAN

By D. R. HOOKER

The glass device shown is held in place over a superficial vein with a soft rubber band until the thin film of collodion placed in the angle formed with the skin has dried. The band is then removed. The pressure required to collapse the vein is recorded by the usual water manometer. The device is an improvement over other methods because it does not slip out of place or leak and because it is small and therefore facilitates, without much inconvenience to the subject, the making of observations during a number of hours. In the event of variations in the illumination of the vein becoming a disturbing factor it is sometimes useful to attach a small lever to the skin over the vein. When the vein is collapsed the lever point descends to an indicator level.



SALINE PERFUSION OF THE SPINAL CENTRES IN FROGS: THE EFFECT OF CALCIUM AND POTASSIUM CHLORIDE

By D. R. HOOKER and S. O. REESE

The decerebrate frog was opened and so far as possible all aortic branches ligated except those supplying the spinal cord. The triceps muscle was used to record reflex response, the stimulus (short tetani) for which was applied to the splanchnic fibres supplying the stomach. The irrigating fluid entered the bulbus and escaped from the great veins.

The effect of potassium is to increase uniformly the irritability of the reflex mechanism. Calcium produces the opposite effect. With the same stimulus, potassium reduces the latent period while calcium prolongs it. When, however, the stimulus bears a definite relationship to the degree of irritability the effect of calcium

seems to be to reduce the latent period below that obtained under the influence of potassium.

SOME PROBLEMS OF GROWTH

By THOMAS B. OSBORNE and LAFAYETTE B. MENDEL

(*a*) **The Capacity to Grow.** — The idea that the capacity to grow inevitably declines and is lost with age has obtained a firm foothold in physiological literature. We have tested the thesis by suppressing the growth of rats and mice for long periods — even far beyond the age at which it is ordinarily completed — without loss of the power subsequently to grow, in rate and extent comparable to what pertains in unchecked development. The retardation has been accomplished by various methods of inappropriate feeding, particularly with qualitatively inadequate proteins in the ration.

(*b*) **The Rôle of Amino-acids in Growth.** — On otherwise adequate diet which contained zein as the sole protein, rats declined rapidly in weight. A quantity of tryptophane equal to 3% of the zein added to the food maintained body weight; further addition of lysine (3%) caused a nearly normal rate of growth. When one-fourth of the zein was replaced by lactalbumin growth was normal. A like addition of casein or edestin induced almost no growth. Addition of tryptophane to the zein-casein diet or of lysine to the zein-edestin diet caused growth nearly equal to that made on the zein-lactalbumin diet. Addition of lysine to a food containing gliadin as its sole protein led to growth at a normal rate.

THE EFFECT OF VAGAL STIMULATION ON THE LOCATION OF THE PACE-MAKER IN THE MAMMALIAN HEART

By WALTER J. MEEK and J. A. E. EYSTER

In some fifty experiments we have verified the findings of Wybau and Lewis that the point of initial negativity in the

mammalian heart at the beginning of each cycle is in the sulcus terminalis immediately over the sino-auricular node.

During vagal stimulation irregular beats may arise from various parts of the heart. The origin of these has been studied by placing non-polarizable electrodes on the sinus node, the superior vena cava, the coronary sulcus as near as possible to the coronary sinus, the atrium of the right auricle, and the ventricular part of the auriculo-ventricular node. By special keys any two of these regions could be compared with each other by connecting them through the string galvanometer. In a series of over two hundred irregular beats appearing during vagal stimulation all but two were found to arise either in the sinus node itself or in some part of the auriculo-ventricular node. The two exceptions arose in the right auricle.

Atrio-ventricular rhythm was produced in twenty experiments by applying formalin, cutting around the sinus node, clamping the node and by stimulating the vagus. Primary negativity of some part of the auriculo-ventricular node was found to be the only absolutely constant criterion of these rhythms. In eight cases the part of the auriculo-ventricular node around the coronary sinus was found to be acting as pace-maker. A coronary sinus rhythm has thus been demonstrated.

Vagal stimulation itself not only occasionally caused atrio-ventricular rhythm, but in such rhythms it often restored the pacemaker to the sinus node provided this organ were only injured or partially isolated. In case the sinus node had been destroyed no other part of the heart could be made to supersede the atrio-ventricular node even on prolonged stimulation. In these cases, however, the pace-maker could be made to shift from the auricular to the ventricular part of the atrio-ventricular node.

With the aid of two galvanometers, one to compare the upper and lower portions of the sinus node and the other to serve as a control between the sinus node and the atrio-ventricular node, it was found that during vagal stimulation the point of impulse formation might pass downward to the lower end of the sinus node. This observation together with the shifting of initial negativity in the auriculo-ventricular node gives a physical basis

for explaining the gradual variations which appear in the As-Vs intervals as atrio-ventricular rhythm comes on.

Our work speaks strongly for the paramount importance of the specialized tissue of the intact mammalian heart in the matter of impulse formation. It also gives some experimental basis for the belief that vagal control is most marked on the most rhythmical part of the specialized tissue that is the upper part of the sinus node. When this is depressed some lower part less under vagal control acts as pace-maker. By increasing the strength of stimulation the whole heart may be finally stopped. On breaking through this inhibition the first beats, as would be expected, are often auriculo-ventricular in nature.

IMMEDIATE AND SUBSEQUENT EFFECTS OF ANAESTHESIA, LOW BLOOD PRESSURE, AND HANDLING OF THE INTESTINES UPON REFLEX CARDIO-INHIBITION

By HOLMES C. JACKSON and E. M. EWING

For the study of variations in irritability of the medullary centres, the reflex cardio-inhibition mechanism was chosen largely on account of the simplicity of its neural architecture and the directness of the muscular response. Examination of the *threshhold value* of this reflex under different conditions was undertaken rather than quantitative variations in responses, either absolute or percentile, as has been done in the case of the vasomotor reflex.

In most instances the results of reflex cardio-inhibition were compared with inhibition of respiration. The mechanism of the later reflex, as is also the case with the vasomotor reflex, is so complicated by unknown factors that the variation in responses may or may not bear a direct or parallel relationship to the acting stimulus.

The left vagus was cut and the central end stimulated with induced currents. Control experiments indicated that during

the course of four hours, the length of experimental procedure, the threshold value remained constant throughout. The threshold was examined under conditions of ether and of morphine anaesthesia, low blood pressure produced by hemorrhage and by partial and temporary ligation of the inferior vena cava, and trauma following severe handling of the intestines.

The following conclusions are warranted:

1. Ether raises and morphine lowers the threshold for this reflex.

2. Low blood pressure from hemorrhage. Pressures not below 60 mm. Hg and continuing for two hours do not alter the threshold; however, as the pressure becomes lower than this, the heart rate usually increases and the inhibitory reflex cannot then be elicited. That this is not entirely due to excessive cardio acceleration is indicated by the fact that where there is only a slight tendency towards increased heart rate, the threshold is also very high. Saline infusion tends to lower the threshold to an extent dependent upon the degree of the hemorrhage and the efficiency of the infusion in bringing the pressure back to normal.

3. Low blood pressure following ligation. Under these conditions the threshold becomes raised only when the pressure becomes as low as 25–40 mm. Hg. The heart rate is not so prone to increase and the threshold returns to normal more quickly upon raising the pressure than in the case of saline infusion following hemorrhage.

4. Dogs, whose pressure had been experimentally reduced by ligation to 40 mm. Hg and held there for two hours, recovered completely.

5. Severe handling of the intestines for two hours raises the threshold after a slight preliminary fall. Following the stoppage of handling, the threshold falls to the normal quite quickly. These statements hold when the pressure remains above 60 mm. Hg. If, following the handling, the circulatory regulation fails and the pressure falls below this figure, then the effects of low pressure influence the result.

OBSERVATIONS ON THE FORMATION OF CEREBROSPINAL FLUID

By F. C. BECHT

The present work was suggested by Dr. J. G. Wilson and is an attempt to secure evidence on the action of pilocarpine on the formation of cerebrospinal fluid, which has been used with good results in certain diseases of the labyrinth.

The method employed is to insert a cannula into the cisterna lying under the ligament extending between the atlas and the occipital bone, tie it into place, and record with a signal magnet the drops as they fall from the cannula. In many cases this method is inadequate and has been replaced by one used by Spina: The fluid is allowed to flow from the cannula into a glass tube with a bore of 1 mm. adjusted to the level of the cannula. The movements of the fluid are recorded in half centimetres from a metre stick upon which the glass tube is mounted.

The results secured do not warrant the belief that pilocarpine has any stimulating effect upon the structures forming the cerebrospinal fluid. It seems probable that the outflow results entirely from vascular changes within the rigid cranium.

The work is being extended to include other substances supposed to have specific effects upon the formation of cerebrospinal fluid.

FURTHER OBSERVATIONS ON THE METABOLISM OF DEPANCREATIZED DOGS

By JOHN R. MURLIN and B. KRAMER

Several experiments intended to ascertain the effects of hydroxyl ions on the output of sugar in the urine were reported. NaOH and Na_2HPO_4 increased the output of sugar per hour and $Ca(OH)_2$ decreased it. Simultaneous effects on the volume of urine indicate, also, that the influence of sodium on the kidney is to increase its permeability and the influence of calcium is to decrease it. This is in agreement with the report of Underhill and Classon.[1]

[1] Underhill and Classon: This journal, 1906, xv, p. 321.

The following experiment was cited as supporting the authors' previously reported negative effects of pancreatic extract on the respiratory metabolism of a depancreatized dog.

June 16	pancreatectomy	
June 19	5.52–6.52 P.M.	R.Q. 0.68
	6.52–7.52	R.Q. 0.71
	8.10 25 gr.	Dextrose by mouth
	9.55–10.55	R.Q. 0.74
	10.55–11.35	R.Q. 0.74

This indicates, possibly, a slight residual capacity to oxidize sugar.

June 20	3.22–4.22 P.M.	R.Q. 0.67
	4.22–5.22	R.Q. 0.69
	5.50–6.45 infused 350 c.c. Ringer's solution containing 1% Na_2CO_3	

During this time an extract of 3 pancreases in Henderson's phosphate mixture was infused by vein.

9.02–10.02	R.Q. 0.75
10.02–11.02	R.Q. 0.78
11.02–12.02	R.Q. 0.72

The increase in R.Q. could be more than accounted for by the Na_2CO_3 (3.5 gr.) administered.

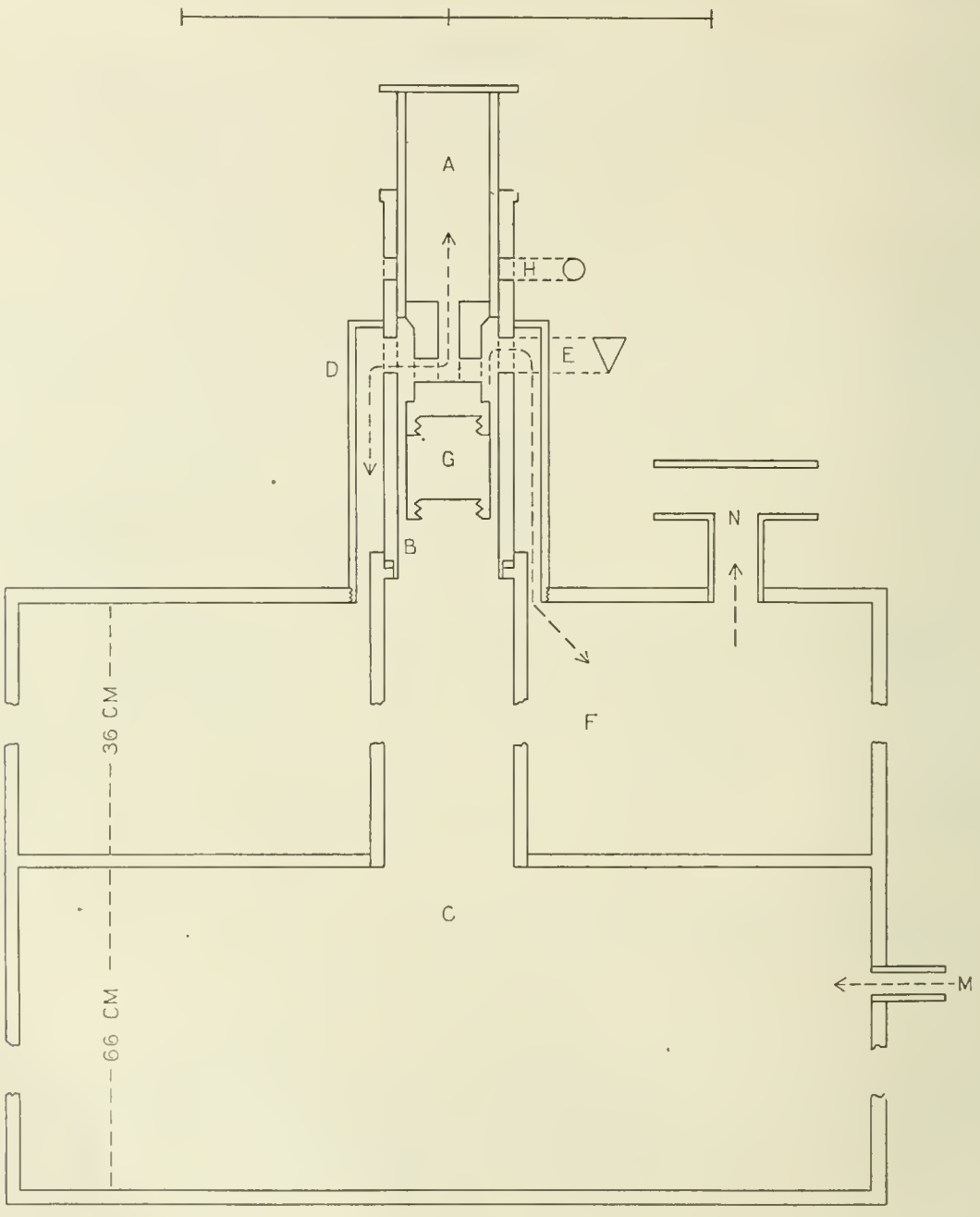
DEVICE FOR INTERRUPTING A CONTINUOUS BLAST OF AIR, DESIGNED ESPECIALLY FOR ARTIFICIAL RESPIRATION

By ROBERT A. GESELL and JOSEPH ERLANGER

In planning this apparatus our object has been to make use of compressed air in laboratories supplied therewith, for the purpose of giving artificial respiration by either the usual or the insufflation method, and in such a way as to render unnecessary the use

of any motive power other than that supplied by the compressed air itself for the purpose of interrupting the blast.

The apparatus consists of the double tank *C* (capacity 10,000



c.c. or more) *F* (capacity 6,000 c.c. or more) and the piston interrupter *G–A*. The air enters *C* through a cock at *M* and, when the piston *A* is down, passes through the pipe *B* alongside the weight *G* into the hollow piston *A*. At a pressure that is determined by the adjustable weight *G*, which is suspended verti-

cally under the point of support of *A*, the piston *A* is raised and so uncovers the paired triangular openings *D–E*. The air then escapes in the direction of the arrows into *F*, whereupon the piston *A* immediately falls back upon its seat closing the orifices *D* and *E*. The tank *F* acts as a buffer to take up the shock due to the sudden entrance of air into it and delivers the air through one of the outlets of *N*, which may be narrowed to further reduce the shock and prolong the escape of air from *F* into the tracheal cannula or catheter. The rate of interruption and the volume and pressure of the air delivered per interruption can be regulated within rather wide limits by adjusting the cock at *M* and the weight *G*. The openings at *H* serve as a safety valve. The piston *A* must fit snugly and work without friction.

EVIDENCES IN THE CEREBRAL CORTEX OF MENTAL EQUIPMENT AND INTELLECTUAL DEVELOPMENT

By E. LINDON MELLUS

As a supplement to results previously published, a report was made of the examination of the cortex of the third frontal convolution, in both hemispheres, of the brain of a former member of the American Physiological Society. This examination fully confirmed the results already reported and it appears probable that the brains of right-handed individuals will show that the cortex of an area surrounding the ascending anterior branch of the fissure of Sylvius is more highly developed on the left than on the right side. In these studies of Broca's area the most marked difference between the two sides is seen in the outer pyramidal and the granular, the second and third layers of Meynert. In these two layers of cells the depth is much greater on the left side, the excess varying from 10 to 60 and even 70 per cent. It is extremely difficult to determine just what has brought about this difference — whether the cells have been forced farther apart by the greater growth of processes and cell connections or whether it may not, in part at least, be due to an increase in the volume of the cells themselves, owing to a growth of the pro-

toplasm enveloping the nucleus. It seems possible that both these causes may contribute to the increase in depth.

Dr. Mellus believes the attempt of Campbell, Brodmann, and others to map out the cerebral cortex into a large number of areas on the strength of slight alleged differences in the type of cortex, representing fixed centres of various functions, is carried to an extreme altogether unwarranted. For one thing, they follow too closely the lines laid down in previous attempts at localization for entire freedom from bias.

In a further study of the brain above referred to, the cortex of the temporal lobe showed no marked differences in the two hemispheres. In comparison with the brains of three Austrian peasants studied in the same manner the cortex of the temporal lobes in the brain of the Professor was much less rich in cells; the cells were on the whole smaller and more scattered and the cortex thinner than that of the same areas in the brains of all three of the peasants. Those brains were from peasants who died in the General Hospital in Vienna and were studied in Prof. Obersteiner's Laboratory.

If we accept the view of those who would map out the cortex into areas of special function, we must look upon the auditory area as one of the most active functionally, at any rate during the early stages of education. In that case we would have to look upon the brain of the peasant as of one gifted naturally with possibilities far beyond those of the Professor. In that case our admiration for what the Professor had accomplished in the face of a heavy handicap would be accompanied by a sense of regret for what the world might have lost in the failure of another to make use of what had been given him.

TWO TYPES OF REFLEX REDUCTION OF BLOOD PRESSURE

By E. G. MARTIN and P. G. STILES

Stimulation of the central end of one vagus in the cat, the other vagus being cut, produces a depression of blood pressure

which varies in amount and in other features with the strength of the stimuli employed. If we note the strength of the shocks by the method of Martin (Z units) we find that when we begin with weak stimuli and increase there is a considerable range within which a small and transient drop of pressure results. This is often no greater when the stimulus is 100 Z than when it is 10 Z or even less. At a rather definite critical level a very much greater and more enduring effect upon pressure is produced. We believe that this level denotes the threshold of the "depressor mechanism" which is thus many times higher than the threshold for the reaction of the mild type. For example, it is a common experience to see a fall of only 6–8% in response to a stimulus rated as 100 or 150 Z and a fall of 25–30% following a stimulus of 200 Z. When this strong effect has been secured little or no additional lowering of pressure can be induced by the most radical intensifying of the stimulation.

THE METABOLIC GRADIENT IN THE NERVE FIBRE

By SHIRO TASHIRO

The different degrees of staining power, of susceptibility to drugs, and of electrical excitability along a nerve fibre strongly suggest the probable existence of different degrees of metabolic activity in the nerve. It was found that there is invariably a metabolic gradient in all nerves, if perfectly uniform fibres are selected. If the claw nerve (mostly efferent) of the spider crab is cut in two, the central portion gives twice as much carbon dioxide production as the peripheral portion. In the case of the afferent, optic nerve of the limulus, an opposite result is obtained, namely, the central portion (near the brain) shows decidely less carbon dioxide production than the peripheral portion. Whether this is due to parallelism between the direction of the normal conduction and the gradient of chemical activity in the nerve fibre, or to a simple embryonic relation between the axis cylinder and the nerve cell (for I have unfortunately chosen the optic

nerve) is not yet decided. The study of some sensory dendrites, now nearly completed, will decide this question.

Whatever may be its correct interpretation, the fact that there is a well-defined metabolic gradient in the nerve fibre may aid in the understanding of some electrical phenomena and of the general nature of nerve impulses.

THE ACTION OF ANAESTHETICS ON CARBON DIOXIDE PRODUCTION IN THE NERVE FIBRE

By SHIRO TASHIRO and H. S. ADAMS

With the view of gaining further evidence of the chemical basis of irritability, the action of various concentrations of anaesthetics upon carbon dioxide production from the claw nerve of the spider crab was investigated. We found that the lower concentrations (1% ethyl urethane and .4% chloral hydrate in sea water) which primarily stimulate the nerve, nearly double the carbon dioxide production of the resting nerve. On the contrary, higher concentrations (4% ethyl urethane and 2% chloral hydrate) which completely anaesthetize the nerve in ten minutes, but restore its excitability, considerably diminish carbon dioxide production of the resting nerve. Similar results are found in the case of the sciatic nerve of the frog and fertilized fish eggs, but quantitative results are not yet quite complete.

SOME PHYSIOLOGICAL FACTORS AFFECTING THE SPEED OF COAGULATION OF THE BLOOD

By W. B. CANNON and W. L. MENDENHALL

Stimulation of the splanchnic nerves is followed by a shorter coagulation time of the blood, which may change from approximately five minutes to approximately two minutes, and may continue at this low level for half an hour. Stimulation of the sciatic

nerve or operation under light anaesthesia has the same result. Excitement, either natural or induced by ether, is accompanied by rapid clotting, but this effect disappears if the splanchnics are severed. If the left adrenal gland is removed, stimulation of the left splanchnic nerve produces either no change or a prolongation of the clotting time; stimulation of the right splanchnic nerve still hastens coagulation. Small doses of adrenalin (.002 mg. per kilo), given intravenously, shorten coagulation. Larger doses (0.05 mg. per kilo) retard coagulation. The small doses have no effect if the circulation is wholly anterior to the diaphragm.

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