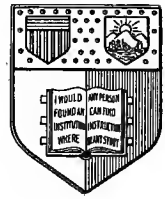


AN

EXPERIMENTAL RESEARCH

ON THE

PHYSIOLOGICAL ACTIONS OF DRUGS

ON THE

SECRETION OF BILE

BY

WILLIAM RUTHERFORD, M.D., F.R.S.

PROFESSOR OF THE INSTITUTES OF MEDICINE (PHYSIOLOGY)
IN THE UNIVERSITY OF EDINBURGH

With one hundred Woodcuts

Reprinted from the JOURNAL OF ANATOMY AND PHYSIOLOGY
and
TRANSACTIONS OF THE ROYAL SOCIETY OF EDINBURGH, VOL. XXIX

EDINBURGH
ADAM AND CHARLES BLACK
MDCCCLXXX

M. W.

NOTE.

The copies of the reprint of this research from the *Transactions of the Royal Society of Edinburgh* having been exhausted, I have been induced to place in the hands of the publishers some copies of the reprint from the *Journal of Anatomy and Physiology*. The arrangement of the reprint in the form of separate papers is explained by the circumstance that they were originally intended for private circulation only.

ERRATA.

Page 45, line 12 from top, *for* "boiling" *read* "bile and."
,, 49 ,, 18 ,, ,, "1872" ,, "1862."
,, 61 ,, 9, after the word "at" *insert* "*b*. The same with 7 grains colocynth injected at."
,, 74 ,, 6 from top, *for* "5 and 6" *read* "48 and 49."

TABLE OF CONTENTS.

EXPERIMENTS ON THE BILIARY SECRETION OF THE DOG, WITH REFERENCE TO THE PHYSIOLOGICAL ACTIONS OF DRUGS.

By WILLIAM RUTHERFORD, M.D., F.R.S., *Professor of the Institutes of Medicine (Physiology) in the University of Edinburgh.* From Experiments performed with the assistance of Monsieur W. VIGNAL and WILLIAM J. DODDS, M.B., D.Sc.

FIRST SERIES.

INTRODUCTION.

(*For References, see end of Memoir.*)

SINCE the liver is an organ whose due activity is indispensable for the maintenance of health; since it is frequently the subject of disorder, and consequently receives a large share of attention from the physician, it is obviously of great importance that he should possess precise knowledge of the manner in which it is affected by medicinal agents.

The physician has had no difficulty in determining when a substance excites the sweat glands, the salivary glands, or the kidneys, but as regards the liver he has been so much embarrassed, that although substances supposed to increase the discharge of bile (cholagogues, χολη, bile; αγω, to drive away) have been administered to man for over 2000 years, there has always been much uncertainty as to those which are really to be regarded as cholagogues; and even in the case of any agent which increases the discharge of bile, he has been quite unable to determine whether this effect is due to a stimulation of the *bile-secreting* or of the *bile-expelling* mechanism.

The reasons for these uncertainties are not difficult to find. The bile, when it enters the intestinal canal, mingles with other secretions, and with alimentary substances, whose quantities are variable. The physician roughly estimates the amount of bile discharged, by observing the colour of the dejections—a method which is of necessity so inaccurate that it is often difficult, sometimes indeed impossible, to say whether or not the discharge of bile is increased, diminished, or unchanged. Thus, when rhubarb is administered, it gives a colour to the dejections similar to that communicated by the bile, and the physician is

therefore puzzled to say whether or not rhubarb affects the liver; yet, by another method of research, it can be shown that rhubarb increases the secretion of bile. Where the substance, as in the case of sodium sulphate, stimulates the intestinal glands, and thus occasions copious dejections of a watery character, whereby their colour is diluted, the physician has found it difficult to say whether or not there is a variation in the quantity of bile discharged; yet, by another method, it can be shown that this substance certainly stimulates the liver as well as the intestinal glands. Again, in the case of such substances as magnesium sulphate and castor oil, which stimulate the intestinal glands but not the liver, the physician, although he certainly did not suppose that they increase the flow of bile, nevertheless failed to observe the fact—which may be shown by another method,—that *they diminish the production of bile.* Again, when a substance excites the liver to produce more bile but does not excite the intestinal glands to pour forth their watery secretion, and as it were to wash out the bile discharged into the canal, the clinical observer has in the case of benzoic acid and its compounds, sodium salicylate and other substances, failed to observe that they are cholagogues. But again, the clinical observer is unable to say whether or not any cholagogue actually stimulates the hepatic cells to produce more bile, or merely excites the muscular fibres of the gall-bladder and bile-ducts to expel their contents. Yet rational medicine imperatively requires that the first of these questions at all events shall receive a definite answer.

There are two methods—the clinical and the physiological—by which the actions of medicinal agents are investigated. On the clinical method, experiments are made on men and animals in a state of disease, with a view to cure the diseased condition; whereas, on the physiological method, experiments are made with drugs on animals and sometimes also on man in a state of health, with a view to determine how they affect the bodily system when its action is not distorted by the influence of disease. The clinical method is as old as medicine itself, but the physiological mode is of comparatively recent date, and has grown out of the fact that the clinical method has proved to have very seriously failed—and nowhere more signally than in the case of the liver—to furnish the physician with that

definite knowledge which is required to bring therapeutics even within sight of the pale of exact science.

Of necessity the influence of a drug upon a diseased condition is the ultimatum of pharmacology, and every experiment upon a healthy bodily system, whether of man or animal, is merely ancillary to experiments with the drug in disease. Therefore, if we discover that a drug stimulates the healthy liver of such an animal as a dog, we do not infer that it must also stimulate the human liver in health, and still less do we conclude that it must also act thus in disease. The experiments on the healthy liver of the dog, on the normal, and on the abnormal human liver, are *three sets of experiments* closely related, but still distinct. The facts derived from any one of the three cannot be substituted for those of the other two. Each set of facts has its own proper place, and must be carefully kept there. When, therefore, we show by the physiological method that such substances as sodium benzoate, sodium salicylate, ammonium phosphate, and others, powerfully stimulate the liver of a dog, we do not for a moment say to the clinical observer, you will find that these things have a similar action in man. We merely say it is likely that they also act thus in man; experiment with them in his case, and tell us if you find that they have on him a similar action, and tell us also in what diseased states you find the employment of this or of that substance most advantageous.

All are agreed that medical science has much to gain from the attainment of a precise knowledge of the physiological actions of medicinal agents. The action of ipecacuan in dysentery is an apt illustration of this fact. On asking a highly experienced Indian physician how he explained the appearance of a large amount of bile in the dejections after the administration of sixty grains of ipecacuan in cases of dysentery, he at once replied, "My theory is that it relieves a spasm of the bile-ducts, and thus allows of the escape of pent-up bile." But, when we give sixty grains of ipecacuan to a healthy dog, it never fails to cause the liver to secrete a greatly increased quantity of bile. Probably, therefore, no one will now be inclined to doubt that in dysentery, ipecacuan affects the liver in a similar manner, and that the increased discharge of bile is due to its increased secretion, and not to the relief of an imaginary spasm of the bile-

ducts. It must be admitted that the attainment of this precise knowledge regarding the action of ipecacuan does not reveal to us the true pathology of dysentery, but it places us one step nearer to a knowledge of it; for, once we know the action of a drug in a healthy state of the body, and find that a diseased state is cured by that action, our knowledge of the nature of the diseased state is necessarily advanced.

While all have admitted the limited and unsatisfactory character of our knowledge of the effects of drugs on the liver, several investigators have attempted to advance the subject by the physiological method of experimenting with drugs on animals. Nearly all the observations have been made on the dog—that being the animal best suited for the purpose. The method resorted to by the earlier experimenters was that of continuously collecting the bile from a *permanent* biliary fistula, and observing how its amount and composition were affected by drugs. A permanent biliary fistula is established by occluding the common bile-duct, and establishing a communication between the fundus of the gall-bladder and the exterior of the abdomen. When the wound in the abdominal wall has completely healed, and nothing remains but the fistulous opening into the gall-bladder, through which all the bile is necessarily discharged, a cannula is placed in the fistulous opening, and the bile collected either in a bag attached to the cannula, or in a large sponge placed in a tin box and secured to the abdomen of the animal. The difficulty of perfectly collecting the bile continuously by day and night, while allowing of such freedom of movement on the part of the animal as is necessary for the maintenance of its health, is so serious that few investigators have succeeded in accomplishing the task. By this method Nasse (1852, *Op.* i.), Kölliker and Müller (1855, *Op.* ii.), and Scott (*Op.* iv.), severally made observations on a single dog with reference to the effect of calomel on the biliary secretion, and the results of their experiments will be detailed under the action of mercury. Being in some measure contradictory, the subject was in 1866 taken up by a committee, of which the late Professor Hughes Bennett was chairman and reporter. Professor Arthur Gamgee and the author were the two junior members of the committee upon whom devolved the task of performing the experiments. The investigation was laborious, and lasted two years. Very great

difficulty was experienced in making a constant collection of the bile extending over a number of days, and it was repeatedly observed, that although the animals were kept on a fixed diet, remarkable variations took place in the amount of bile secreted daily, when no cause could be assigned.

This circumstance rendered the method of experiment one from which it was difficult to arrive at just conclusions; nevertheless the experiments seemed to warrant the statement that "spontaneous diarrhœa, dysentery, and purgation produced by pilula hydrargyri, calomel, corrosive sublimate, and podophyllin diminished the solid constitutents of bile, and, with one exception, the fluid portion of the bile also" (*British Association Reports*, 1868, p. 229).

These are indeed meagre results, considering the great labour which their attainment entailed, and it must be admitted that they were to some extent misleading; not because of any inaccuracy of observation, but because the method of experiment was not adapted to supply, at brief successive periods of time, information regarding the state of the secretion of bile. On that account it failed to show that in the case of such a substance as podophyllin—which certainly increases the biliary secretion, but which also stimulates the intestinal glands—if too large a dose be given, the effect on the liver may be overcome by its effect on the intestine, and a diminished secretion of bile result. (See Experiment 9 in the sequel.)

In 1873 Röhrig (*Op.* vi.) reopened the investigation of this subject. He observed the rate of biliary flow from *temporary* fistulæ in fasting curarised dogs before and after the injection of purgative agents into the stomach or intestine. He found that large doses of croton oil greatly increased the secretion of bile, and that a similar effect, though to a less extent, was produced by colocynth, jalap, aloes, rhubarb and senna, and sulphate of magnesia—the potency of these agents as stimulants of the liver being in the order mentioned. He found, moreover, that castor oil had little effect, and that calomel, while it seldom recalled the biliary secretion after it had ceased, nevertheless somewhat augmented it when it was taking place slowly.

Röhrig's statement with regard to calomel does not much differ from that made by Hughes Bennett's committee, but nevertheless he did find that certain purgative agents, when

given to *fasting* animals with temporary biliary fistulæ, increased the biliary secretion, while the committee found that in *non-fasting* animals with permanent fistulæ, purgative action, induced by podophyllin, calomel, &c., diminished the amount of bile secreted in the twenty-four hours.

It appeared to me that this important subject could not be allowed to remain in a position so unsatisfactory. I therefore entered on the following research, but ere I had proceeded very far I found its labours so excessive, that I was glad to avail myself of the very valuable assistance of my pupils, Monsieur W. Vignal, and latterly of Dr William Dodds, in performing the experiments.

Method of Experiment.

All the experiments recorded in the following pages were performed on dogs. The dog was selected—1. Because the size of its common bile-duct renders it possible to introduce a cannula with an orifice sufficiently large to prevent its being blocked up by particles of inspissated mucus from the gall-bladder. 2. For the reason that its digestion resembles that of man, inasmuch as its stomach becomes empty when the process is completed. It is very different in the case of a rabbit, whose stomach is never empty. 3. As Röhrig had performed his experiments on dogs, it was necessary that we should compare our results with his. The selection of the dog has proved fortunate, for the results of our experiments are in complete harmony with every perfectly ascertained fact regarding the actions of medicinal agents on the human liver, and prove that the liver of this animal is affected in the same sense—although it may not be to the same degree—by substances that act on the human liver. All the experiments having been performed on animals of the same species, placed as nearly as possible under similar conditions, the results are fairly comparable; although it must be borne in mind that just as no two members of the human species can even in their normal condition be regarded as equally susceptible to the influence of any medicinal agent, neither can any two members of the canine species be held to possess identical susceptibilities. All the animals had a full meal of lean meat at three or four o'clock in the afternoon, and the experiment was begun between nine and ten o'clock on the

following morning, so that the digestion and absorption of the food were completed, and the animal was therefore in a fasting condition. This was an essential preliminary; for, as is well known, the secretion of bile is accelerated during the process of digestion, and had we taken the amount of bile secreted per hour during digestion, as an index of the activity of the liver previous to the administration of a drug, our experiments would necessarily have been worthless. The disturbing effect of irregular muscular movements upon the biliary flow was prevented by injecting into a vein small doses of curara, repeated at intervals, when the motor paralysis which it induces became too slight. In consequence of the curara palsy, artificial respiration was had recourse to, and maintained at regular intervals throughout the whole experiment. Chloroform was used during the preliminary operation in two cases, but the stimulation of the liver which it induced rendered the experiments worthless.[1] On the other hand, we have abundantly proved that the doses of curara administered in the following experiments have no influence on the biliary secretion, and do not interfere with the effects of hepatic stimulants. It is therefore an exceedingly valuable auxiliary in a research of this nature. The method of experiment we adopted was always that of a *temporary* biliary fistula. Through an opening in the linea alba a glass cannula was inserted into the common bile-duct near to its junction with the duodenum, and tied therein. To the end of the cannula projecting from the abdomen a short caoutchouc tube was attached, and to the free end of this a short glass tube drawn to a narrow aperture so that the bile might drop from it, as Röhrig (*Op.* vi.) had recommended. The gall-bladder was then compressed, in order to fill the whole tubing with bile, and the cystic duct was clamped to prevent its return to the gall-bladder, and so compel all the bile secreted

[1] It may be well to state, however, that in all the operations for the previous experiments on the action of cholagogues performed by me twelve years ago, at a time when there was no antiphysiological excitement prevailing, chloroform was fully administered to every animal, because in those experiments the biliary fistula was of a permanent nature, and observations were not begun on the biliary secretion until some days after the operation—when of course the effect of the chloroform had completely passed off. The biliary fistula being of a temporary character in the present research, and the whole time taken up by each experiment being not more than a few hours, the use of anæsthetics was inadmissible.

by the liver to flow through the cannula. The wound in the abdominal wall was then carefully closed, and in all save the earliest experiments the animal was thoroughly covered with cotton wool, in order to quickly restore it to its normal temperature; and, guided by a thermometer in the abdominal cavity, great care was taken to keep the temperature normal,—a matter of no small importance,—for if the temperature fall several degrees, the liver secretes more slowly.

The respiration requires to be maintained with regularity, otherwise the biliary flow is rendered somewhat unequal by irregular diaphragmatic compression of the liver. Moreover, if the respiration be deficient, the secretion of bile is always diminished. Some of the slight oscillations observable in the charts of the biliary secretion in these experiments are probably owing to variations in the respiration; for in the earlier experiments we were obliged to have the respiratory bellows moved by the hand, and this is never so regular as a machine. Notwithstanding this, however, the main results of these experiments are perfectly clear.

Until it is attempted, one might suppose that this mode of experiment is extremely simple, but it is by no means so simple as it appears. It is needful to manipulate the abdominal viscera with great care, and to avoid all dragging at the bile-duct, otherwise the secretion of bile becomes so irregular that the experiment may be useless. The cannula must be very carefully retained in a position which will permit of its moving with the diaphragm, but will prevent it from twisting the duct, and thus impeding the exit of the bile by forming a valve at its orifice.

Röhrig estimated the velocity of the biliary secretion by counting the seconds that elapsed between the fall of the drops from the orifice of the tube. A single trial convinced us that this method is extremely laborious, and leads to inaccurate results, because it does not permit of continuous observation for any length of time. Variations in secretion often occur independently of the administration of any substance, and it is impossible to estimate their significance, and make due allowance for them, unless the method of continuous collection of the bile be adopted. Moreover, we saw that the degree of viscosity of the bile caused a variation in the size of the drops,

and, therefore, in the intervals between their fall. We therefore abandoned this for the more accurate method of allowing the bile to flow into a fine cubic centimeter measure, and recording the quantity secreted every quarter of an hour. In addition to constant collection of the bile, this method has the great advantage of permitting a graphic representation of the results.

It is evident from the method of experiment that all our observations relate exclusively to the effects of substances on the *bile-secreting* mechanism. We have made no observations regarding their effects on the *bile-expelling* mechanism. Nor do we intend to prosecute the latter part of the inquiry, for the question, what substances stimulate the liver to secrete more bile, is of infinitely greater importance. We shall be able to give to it a precise answer, and thus for the first time to furnish the physician with definite knowledge for his guidance in the treatment of hepatic disorder.

In several instances we analysed the bile secreted before and after the administration of a drug; but although valuable facts were thus ascertained, we found that in consequence of the excessive labour of this research it was impossible to analyse the bile in all cases. We therefore discontinued the analyses, after observing that even when a hepatic stimulant renders the bile more watery, the increased velocity of secretion always more than compensates the diminution of the solids, and thus compels the liver to produce in a given time a larger amount of the biliary constituents proper.

We were also at the pains to make in most cases *post-mortem* examinations of the small and sometimes of the large intestines and stomach, in order to compare the effect of the drug on the liver with its effect on the intestine. The results are valuable, because—1. They furnish for the first time a systematic account of the effects of well-known and also of many new drugs upon the intestinal mucous membrane; 2. By separating the secretion of the liver from that of the intestinal glands, a more exact knowledge of the effects of substances on the latter is obtained, and a very important generalisation regarding the effect on the secretion of the bile, produced by stimulating the intestinal glands, has been arrived at, as will be shown in the sequel. It ought to be observed that some of the substances may perhaps

have stimulated the pancreas, and as the pancreatic duct was never tied, the fluid in the intestinal canal may have been a mixture of intestinal and pancreatic juices. But as the liver was the primary object of our investigations, it would have been altogether unjustifiable to have set up more irritation at the duodenum, by cutting down on the pancreatic duct and placing a cannula in it—always a difficult thing to do in the dog, and apt to involve a good deal of hæmorrhage. Although by such a procedure, definite knowledge might have been arrived at with regard to what substances affect the pancreas, yet our results as regards the liver—a gland of greater importance in the economy,—might have been vitiated. Probably in most cases the fluid found in the intestine was chiefly intestinal juice, but for the reason mentioned no conclusive statement is permissible with regard to this point.

The small doses of curara given to the animals were injected into the jugular vein, in order that their effect might be speedy; but nearly all the drugs given for the purpose of affecting the liver or intestine were injected into the duodenum, because the animals being curarised could not swallow, and the penetration of the duodenal wall by the sharp nozzle of a small syringe was a much simpler operation than the introduction of a tube down the œsophagus into the stomach. Moreover, the stomach in a dog that has fasted for many hours usually contains a large quantity of mucus that must have retarded the absorption of the substance if given by the mouth. To avoid this delay was a matter of great importance, both on the animal's account, and also because of the impossibility of continuing the experiment for more than a few hours. Moreover, it has been alleged that the action of a cholagogue may be due to a reflex excitement of the liver proceeding from the duodenal mucous membrane; therefore by always injecting the substances into the duodenum we ensured its action—if any—on this portion of the intestine. It must of course be borne in mind, that when a drug is placed in the duodenum directly, and a certain effect on the liver ensues, it by no means follows that the same effect will accrue, if the drug be placed in the stomach and thus come in contact with the gastric juice. But the general harmony of the results of our injecting substances into the duodenum, with those

observed in man when the drugs are taken by the mouth, convinces us that our method is reliable. In only one instance indeed—that of calomel—did it seem probable that its having escaped the influence of the gastric juice was vitiating the result, for the hydrochloric acid of the juice can convert calomel into corrosive sublimate, and we have discovered that while calomel does not, corrosive sublimate does, stimulate the liver. A discussion of that case will be found under the action of mercury, and we think it the only one that needs special consideration.

Secretion of Bile in a Curarised Fasting Dog.

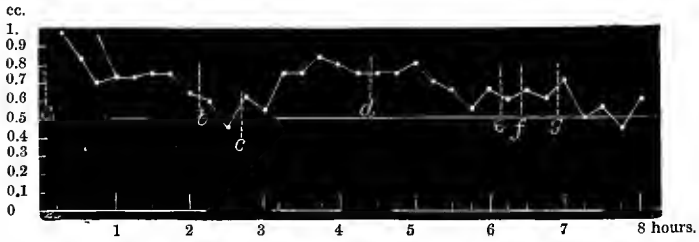
It was of course necessary—as a preliminary step—to observe the amount of bile secreted in the course of a day by a dog that had fasted about eighteen hours, and to which nothing but curara was administered. The solution of curara employed in all the experiments was a filtered aqueous solution, every minim of which contained one milligramme of the poison. The solution was always injected into the jugular vein.

In all the woodcuts the numbers under the abscissa indicate the hours during which the secretion of bile was observed, while those to the left of the ordinate indicate in cubic centimeters the amount of bile which flowed from the cannula; the dots in the curve indicate the quantities of bile collected every quarter of an hour. The vertical dotted lines that cross the curves in the illustrations indicate that something was given to the animal. In all such experiments the amount of bile first collected is usually much greater than that at subsequent periods. This apparently results from the sudden diminution in the resistance to the exit of the bile consequent upon opening of the duct. The first one or two collections are therefore not reliable indices of secretion, and they are therefore omitted from some of the charts.

Experiment 1. Dog that had fasted 18 hours. Weight 7·6 kilogrammes.—Twenty milligrammes of curara were injected into jugular vein (at *a*, fig. 1). The abdomen was then opened, and the cannula placed in the common bile-duct, as above indicated. The wound in the abdomen was closed, the

animal enveloped in cotton wadding, and the bile collected. As the experiment proceeded, the effect of the curara gradually

Fig. 1.

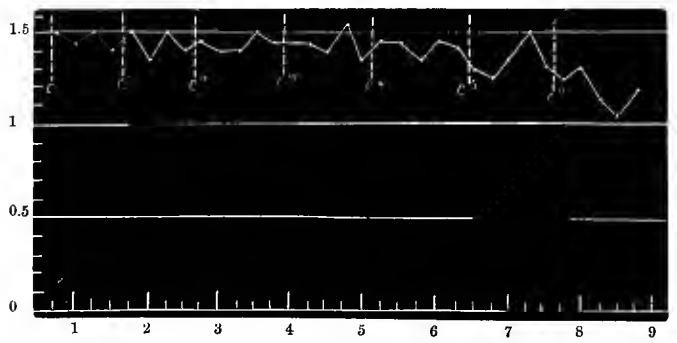


Secretion of bile by a fasting dog with nothing but curara administered. *a*. 20 mill. ; *b*. 2 mill. ; *c*. and *d*. 4 mill. ; *e*, *f*, *g*. 3 mill. curara injected into jugular vein.

wore off, owing to its elimination, and it was necessary to inject from two to four *milligrammes* from time to time (*b*, *c*, *d*, *e*, *f*, *g*, Fig. 1). If the curve be examined, it will be observed that these doses had no apparent effect on the biliary secretion, which was in this case tolerably regular. After falling until the middle of the third hour, it increased for a time and then fell somewhat. At the eighth hour it was slightly below what it had been at the close of the first.

Experiment 1A. Dog that had fasted 17 hours. Weight 18.7 kilogrammes. (Fig. 1A.)

Fig. 1 A.



Secretion of bile by a fasting dog with nothing but curara administered. 20 mill. given at *c*, 4 mill. given at *c'*, *c''*, *c'''*, *c*^{4}, *c*^{5}, 3 mill. given at *c*^{6}.

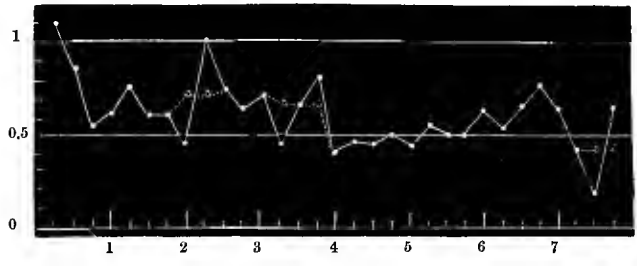
As it is evident from these two experiments that doses of curara such as those given above do not apparently affect the biliary secretion, the times at which they were given are not indicated in any of the subsequent charts, for in all cases curara was given as above indicated. The great value of this substance in this connection is, that while not obviously affecting biliary secretion, as chloroform does, it paralyses voluntary movement, and thus prevents the irregular outflow of the bile that ensues when the abdominal muscles contract.

The analysis of the bile in such a case as the above having been omitted, another experiment was performed for the purpose of supplying the want.

Experiment 2. Dog that had fasted 19 hours. Weight 15 kilogrammes.—Nothing was given but curara in doses similar to those above mentioned. (Fig. 2.)

The biliary flow was not so regular in this as in the previous cases. The mean has been taken, and triangles with dotted lines are superadded in the Fig. for the purpose of indicating the probable position of the *dots* had the secretion been regular.

Fig. 2.



Secretion of bile in a fasting dog with nothing but curara administered.

This was done on the supposition—entertained until more experience was gained—that these irregularities in the curve were due, not to variation in *secretion*, but to irregularity of *outflow*, owing to a variation in the facility with which the bile could enter the cannula. It was in time ascertained, however, that an irregular curve generally ensued when there was much difficulty in inserting the cannula into the duct, and the latter had to be a good deal pulled about, in consequence of

which the liver probably suffered somewhat from nervous irritation.

Composition of Bile in a Fasting Dog.

Analyses were made of the bile secreted by the second dog during the first, fourth, and last hours of the experiment. The following are the results :—

Table I.—*Composition of Bile secreted by a Dog paralysed by Curara after fasting nineteen hours.*

Experiment 2.	Bile secreted during		
	First Hour.	Fourth Hour.	Last Hour.
Water	89.53	89.58	89.55
Bile-acids, pigments, cholesterin, fats	8.73	8.68	8.71
Mucus	0.71	0.72	0.72
Ash	1.03	1.02	1.02
Total	100.00	100.00	100.00

It therefore appears that in the progress of the experiment the composition of the bile remained almost precisely the same. This is remarkable, seeing that the animal had been deprived of water for so long a time, and, moreover, seeing that the entrance of the bile into the intestine had been cut off. It should be mentioned that in taking the bile secreted near the beginning of such experiments for analysis, we were always careful to eliminate that which had been expressed from the gall-bladder into the cannula.

Secretion of Bile per Kilogramme of Body-weight in a Fasting Condition.

The absolute quantity of bile secreted by different individuals varies with the size of the animal; therefore, in order to ascertain the amount of work that is really done by the liver in any case, it is necessary to know the quantity of bile secreted per kilogramme weight of the animal in a unit of time. In all these experiments, therefore, the animals were

weighed, so that the secretion of bile per kilogramme might be determined.

Experiment 1.		Experiment 1A.		Experiment 2.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
1.0		1.5		1.1	
0.85		1.47		0.85	
0.7		1.5		0.55	
0.75		1.4		0.6	
0.75	0.394	1.5	0.307	0.75	0.17
0.75		1.35		0.6	
0.75		1.5		0.6	
0.65		1.4		0.45	
0.6	0.309	1.42	0.3	1.0	0.19
0.45		1.4		0.75	
0.65		1.4		0.65	
0.55		1.5		0.7	
0.75	0.381	1.47	0.312	0.45	0.177
0.75		1.45		0.65	
0.85		1.42		0.8	
0.8		1.4		0.4	
0.77	0.393	1.52	0.305	0.45	0.12
0.77		1.37		0.45	
0.75		1.42		0.5	
0.8		1.42		0.45	
0.7	0.355	1.37	0.301	0.55	0.133
0.65		1.45		0.5	
0.55		1.4		0.5	
0.65		1.3		0.62	
0.6	0.328	1.27	0.288	0.55	0.168
0.65		1.32		0.6	
0.6		1.5		0.75	
0.7		1.3		0.65	
0.5	0.292	1.25	0.267	0.4	0.123
0.55		1.3		0.15	
0.47		1.15		0.65	
0.6		1.05			
	Mean. 0.351 cc.	1.2	*Mean.* 0.254 cc.		*Mean.* 0.154 cc.

In the three curara experiments detailed above, the mean secretion per kilogramme weight of the animal was 0.351 cc. in Exp. 1, 0.254 cc. in Exp. 1A, and 0.154 cc. in Exp. 2. In the first case, the secretion was, from some unknown cause, unusually high: the last two figures will be found a much nearer indication of what is usual in the fasting animal, but in subsequent experiments it will be seen that the secretion is frequently below even the small figure in Exp. 2.

Undoubtedly, the true test of hepatic work is the amount of bile-*solids* secreted per unit of animal weight, in a unit of time. Any one may calculate this from the analyses, but inasmuch as these were not made in every case, and seeing that we have found that whenever a substance increases the biliary secretion, it augments the excretion of bile-solids by the liver, even although the bile be rendered more watery, we have thought that a statement of the amount of *fluid bile* secreted per kilogramme of dog will be sufficiently refined for the purpose of this research, because the question we have set ourselves to answer is principally this: What substances have the power of exciting the secreting apparatus of the liver? a question which cannot be answered by the ordinary observations on man, for there it is impossible to determine whether an increased amount of biliary matter in the dejections is due (1) To contraction of the gall-bladder, and larger bile-ducts. (2) To the relief of some possible spasm of the larger bile-ducts, or (3) To an increased secretion by the liver.

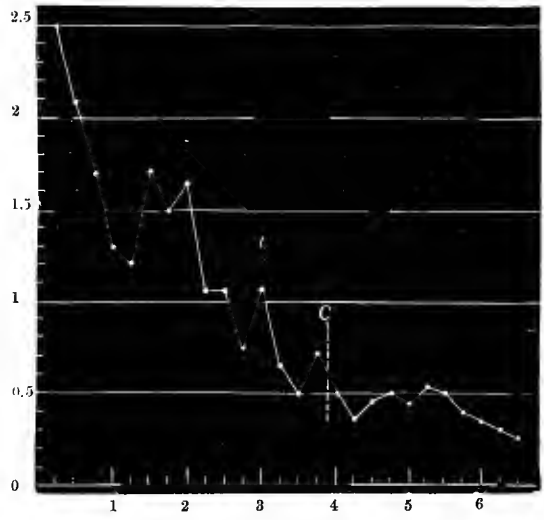
A second question before us is the relative powers as hepatic stimulants of the various substances employed. Our answer to this can only be approximative, for it would require a considerable number of experiments with any one substance to ascertain the most effective dose in the dog. This would entail an amount of suffering and of labour that seems altogether unwarranted by the result to be attained. We therefore believe that we do enough if we give a definite answer to the first of our questions, and an approximative answer to the second. The latter will be fairly well given by determining the amount of bile secreted per kilogramme weight of the animal per hour.

Action of Croton Oil.

Röhrig has placed croton oil at the head of his list of hepatic stimulants, with the statement that in doses from eighteen drops to a "teaspoonful" it has an exciting effect on the biliary secretion even under the most unfavourable circumstances (*Op.* vi. p. 250). This substance was therefore made the subject of our first experiments with cholagogues.

Experiment 3. Dog weighing 7.3 kilogrammes.—Considering the small size of this dog, the secretion of bile was unusually great. This probably resulted from digestion being incomplete; for, although the animal was fed seventeen hours before the experiment, at death a quantity of elastic tissue, and a greyish fluid resembling chyme, were found in the stomach. After the secretion had fallen very low, fifteen grains (about thirty drops) of croton oil, in sixty minims of almond oil, were injected directly into the duodenum (at *c*, Fig. 3). The dose was a large one, but not so large nor yet so small as the quan-

Fig. 3.



Secretion of bile when digestion was incomplete. Fifteen grains croton oil injected into duodenum at *c*.

tities given by Röhrig. After half-an-hour, the fall in the bile-secretion was arrested, and a slight rise took place. Towards the close of the experiment, the pulse became extremely weak.

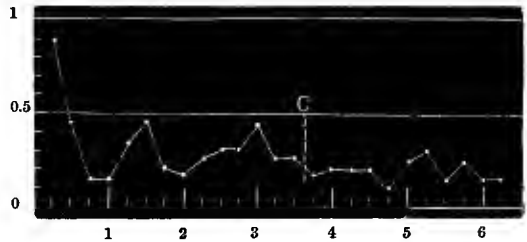
Autopsy.[1]—The mucous membrane of the upper three-fourths of the small intestine was intensely red, especially in the duodenum, the colour of which resembled that of claret.

[1] In all cases, unless otherwise stated, the autopsy was performed immediately at the close of the experiment.

There was evidence of impending purgation in the small intestine. The weak pulse at the close of this experiment, together with the violent intestinal irritation, suggested that the collapse had been occasioned by the drug, and that a smaller dose should be given in the next experiment.

Experiment 4. Dog weighing 5.9 kilogrammes.—This animal had refused almost all food for nearly two days. Six grains of croton oil in sixty minims of almond oil were injected into the duodenum (*c*, Fig. 4). No increase of the biliary secretion followed. The pulse became so weak that the experiment was ended two hours and a half after the oil was given.

Fig. 4.



Secretion of bile before and after six grains of croton oil were injected into duodenum at *c*.

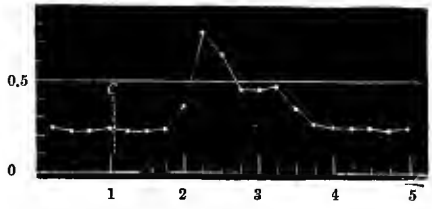
NECROPSY.—The oil had found its way into the stomach. The gastric mucous membrane was of a claret colour. There was slight redness of the duodenum, but no evidence of purgative action.

Experiment 5. Dog that had fasted 18 hours. Weight 3.1 kilogrammes.—In this experiment, only three grains croton oil in sixty minims almond oil were injected into the duodenum. A decided increase in the biliary secretion began within an hour after the injection. The secretion soon reached a maximum, and then fell in the course of two hours to the same level as before the injection. (Fig. 5.)

NECROPSY.—A portion of the oil was found in the stomach, and another portion half way down the small intestine. The gastric mucous membrane was intensely red. There were patches of slight redness here and there in the duodenum. No evidence of purgative action.

These experiments were undertaken simply to test the accuracy of Röhrig's conclusion arrived at by his method of

Fig. 5.



The secretion of bile before and after three grains of croton oil were injected into the duodenum at *c*.

counting the drops of bile. Our method, which, as we have explained, is more reliable, gives no evidence that croton oil is to be regarded as a potent cholagogue, and, seeing that it has no reputation as such in practical medicine, we deemed further experimentation with it uncalled for.

That there was no purgation from these doses of croton oil is a singular fact, which has been laid hold of by some persons as evidence that medicines affect the dog and man very differently, and that therefore the results seen in the one cannot be applied to the other. It is well known, however, that a difference in action is *quite exceptional*, and certainly the following experiments fully bear out this opinion. The only explanation of the non-purgative action of the oil in the above cases that suggests itself is, that possibly too great a dose of this violent irritant was introduced into the intestine, and that a paralysis of Lieberkühn's follicles was the result. The large doses were given in imitation of Röhrig's experiments.

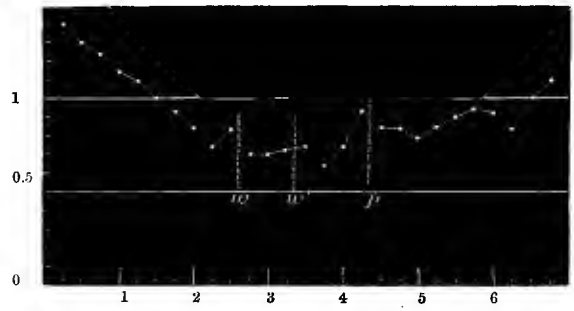
Action of Podophylline.

Experiment 6. Dog that had fasted 19 hours. Weight 15.3 kilogrammes.—The secretion of bile fell very gradually (Fig. 6). Ten cubic centimeters of water were injected into the duodenum at *w*. There being no apparent effect, 100 cc. were injected at *w'*. The slight rise in secretion that ensued at the end of an hour may have been owing to this; but it is not likely, seeing that water is absorbed with rapidity. At *p*, ten grains

podophylline, suspended in 10 cc. water, were injected into the duodenum; and it is probable that the rise in secretion two hours afterwards was due to the podophylline.

NECROPSY.—The mucous membrane of the duodenum, and to a slight extent below it, was very vascular, and this part of the

Fig. 6.

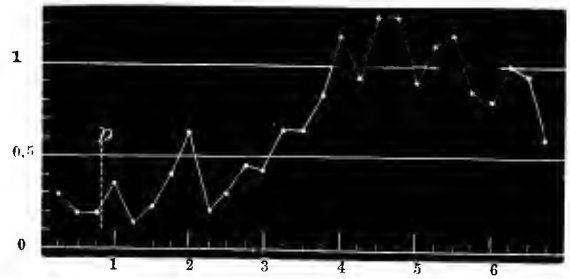


Secretion of bile before and after water and podophylline. *w*. 10 cc. water; *w'*. 100 cc. water; *p*. 10 grains resina podophylli in 10 cc. water injected into duodenum.

intestine contained a considerable quantity of a slightly brown fluid, thereby affording evidence of a purgative effect.

Experiment 7. Small dog that had fasted 19 hours.—Eight grains podophylline in 25 cc. water injected into duodenum (*p*, Fig. 7). The subsequent increase in the biliary secretion

Fig. 7.



Secretion of bile before and after eight grains of resina podophylli in 25 cc. water were injected into duodenum at *p*.

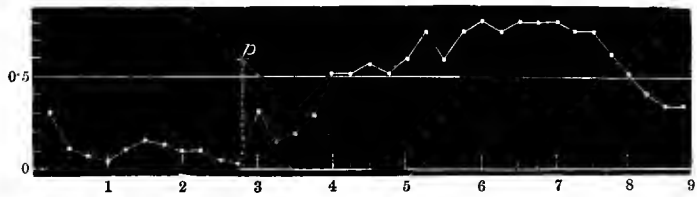
was most marked about four hours after administration, but by the end of the sixth hour the effect had greatly diminished.

NECROPSY.—Upper part of small intestine contained a viscous brownish fluid. As the small quantity of water injected had probably been absorbed, the intestinal contents were regarded as distinct, though not abundant, evidence of purgative action. The mucous membrane, to the extent of about eighteen inches below the pylorus, was extremely vascular. The remainder of the intestine was pale. A small quantity of mucus was found in the stomach, the mucous membrane of which was pale.

Experiment 8. Dog that had fasted 18 hours. Weight 6.6 kilogrammes.—Six grains podophylline in 9 cc. water injected into duodenum (*p*, Fig. 8). The subsequent rise in the bile-secretion is very evident. The secretion attained its maximum between three and four hours after the administration of the podophylline. As in the previous case, the effect on the liver had very greatly diminished by the end of the sixth hour after administration.

NECROPSY.—Distinct, though not abundant, evidence of purgative action in small intestine, and decidedly increased vascularity of the mucous membrane in its upper two-thirds. Nothing remarkable in stomach or large intestine.

Fig. 8.



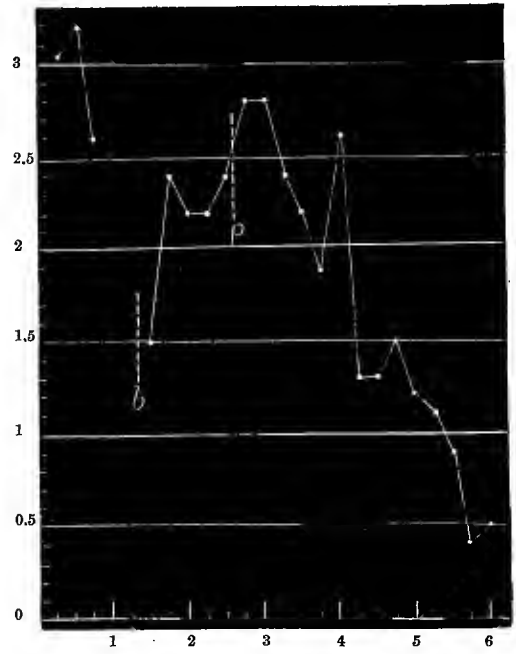
Secretion of bile before and after six grains of resina podophylli in 9 cc. water were injected into duodenum at *p*.

Probably every one will be struck by the slowness and the small extent of the purgative action in these experiments, notwithstanding the large doses of podophylline. That this was owing to the insolubility of podophylline in water is probable, from the two following experiments. Zwicke, Hagentorn, and Köhler having shown (*Op.* vii.) that convolvulin, elaterin, and some other substances have no purgative action unless they come in contact with bile—which, therefore, appears to be a

solvent for them—it occurred to us that the tardy action of the podophylline might be owing to the non-entrance of the bile into the intestine. Accordingly in the next experiment the podophylline was suspended in bile.

Experiment 9. Dog that had fasted 18 hours. Weight 11 kilogrammes.—12.2 cc. bile injected into duodenum (*b*, Fig, 9). Unfortunately, there is a hiatus in the curve immediately before the injection, owing to a loss of the bile; nevertheless it is

Fig. 9.



Secretion of bile before and after podophylline. *b*. 12.2 cc. bile; *p*, nine grains resina podophylli in 12 cc. bile injected into duodenum.

evident that increased bile-secretion followed the injection when the biliary flow had become fairly constant. Nine grains podophylline, triturated in a mortar with 12 cc. bile, were injected into the duodenum (*p*). A rapid increase in the bile-secretion ensued; but it soon diminished, and three hours after the injection it was lower than it had ever been. In this remarkable experiment, therefore, the *diminution* of bile-

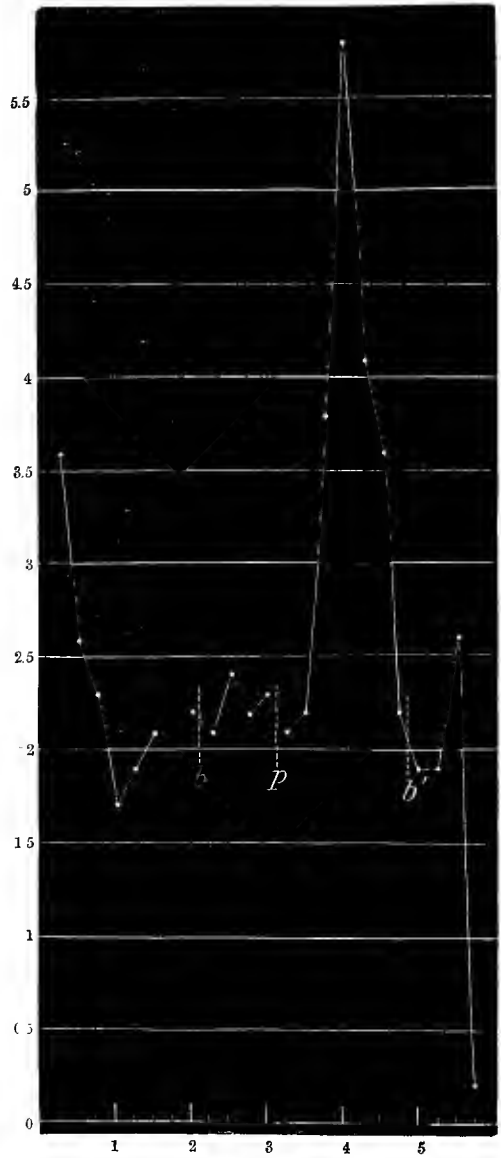
secretion after podophylline was far more remarkable than its increase; indeed, the increase might possibly have been owing to the injected bile, and not to the podophylline. Towards the close of the experiment the pulse became weak, but not excessively so.

AUTOPSY.—Mucous membrane of stomach and whole length of small intestine intensely red. The small intestine contained a large quantity of fluid. The large intestine contained a considerable quantity of liquid fæcal matters. There was, therefore, abundant evidence that excessive purgation was imminent.

In this experiment, the intestinal irritation and the purgative effect were far greater than they were in any of the previous experiments with podophylline, and it is evident that the principal change in the bile-secretion was *diminution*. It therefore appeared that, with a powerful solvent such as the bile, nine grains of podophylline produced a too violent effect upon the alimentary canal. The previous experiments having shown that, with a slighter action on the intestine, there was a more powerful action on the liver, suggested that with a smaller dose of podophylline given in the biliary solvent, an action on the liver would be evident, and that this would follow the injection more speedily than it had done in the experiments where the podophylline was not given in a state of solution. The next experiment realised this anticipation in a very striking manner.

Experiment 10. Dog that had fasted 19 hours. Weight 17.1 kilogrammes.—The bile-secretion was about 2 cc. per fifteen minutes before injection into the duodenum of 6 cc. bile and 6 cc. of water, *b*, Fig. 10. The subsequent increase of secretion was trivial. An hour after this, four grains podophylline, in the same quantity of bile and water, were injected (*p*). About half an hour afterwards a great acceleration of the biliary flow began, and lasted about an hour. In one of the periods of fifteen minutes, no less than 5.8 cc. of bile were secreted; a quantity never noticed in any other experiment, even on larger dogs. When this great hepatic excitement had disappeared, 6 cc. of bile and 6 cc. of water were again injected (*b'*), as in the first instance. The fall in the secretion was for a time arrested; but within three hours after the administration

Fig. 10.



Secretion of bile before and after podophylline. 6 cc. bile and 6 cc. water injected into duodenum at *b*. and *b'*. Four grains podophylline in the same fluids injected at *p*.

of the podophylline, the action of the liver had almost entirely ceased. The pulse was weak, but not extremely so.

AUTOPSY.—The mucous membrane of the duodenum was intensely vascular, but that of the remainder of the small intestine did not show an increased vascularity nearly so great as in the previous experiment. The upper three-fourths of the small intestine contained very decided evidence of purgative effect. The gastric mucous membrane had a dull red appearance.

Experiment 8.		Experiment 9.		Experiment 10.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
0.3		3.05		3.6	
0.1		3.2		2.6	
0.07		2.6		2.3	
0.05		lost.		1.7	
0.1		lost.		1.9	
0.15		*b* ——		2.1	
0.12		1.5		lost.	
0.1		2.4		2.2	
0.1		2.2	0.836	*b* ——	
0.05	0.042	2.2		2.1	
0.03		2.4		2.4	0.526
p ——		*p* ——		2.2	
0.32		2.8		2.3	
0.15		2.8	0.927	*p* ——	
0.2		2.4		2.1	
0.27		2.2		2.2	
0.52		1.9		3.8	
0.52		2.6	0.645	5.8	1.01
0.57		1.3		4.1	
0.52		1.3		3.6	
0.6		1.5		2.2	
0.75		1.2	0.427	*b′* ——	
0.6		1.1		1.9	
0.75		0.9		1.9	
0.8		0.4		2.6	
0.75		0.5		0.2	
0.8	0.477				
0.8					
0.8					
0.75					
0.75					
0.62					
0.52					
0.42					
0.35					
0.35					

Composition of Bile before and after Podophylline.

The next question to be answered was evidently this, is the increase in the quantity of bile after podophylline merely due to an increase of water, or are the bile-solids also increased? The bile secreted by dog 10, between the second hour and a half and the third hour, and that secreted an hour and a quarter after the administration of podophylline, were analysed with the following results. (Table II.)

TABLE II.—*Podophylline.*

Experiment 10.	Before.	After.
Water	90.83	91.07
Bile-acids, pigments, cholesterine, fats	7.75	7.84
Mucus	1.00	0.60
Ash	0.42	0.49
	100.00	100.00
Velocity of secretion per half-hour	4.6 cc.	9.6 cc.

It thus appears that, notwithstanding the great velocity of bile-formation, the special bile-solids were not diminished; the only noteworthy diminution being in the amount of mucus. This remarkable result was confirmed by the following analysis of the bile in another case. (Table III.)

TABLE III.—*Podophylline.*

Experiment 10 A.	Before.	After.
Water	94.26	94.28
Bile-acids, pigments, fats, cholesterine	4.66	4.68
Mucus	0.73	0.70
Ash	0.35	0.34
	100.00	100.00
Velocity of secretion per half-hour	1.86 cc.	2.47 cc.

Results of the Experiments with Podophylline.—1. Podophylline, when injected into the duodenum of a fasting dog, increases the *secretion* of bile. It is inferred that the increased biliary flow in the preceding experiments was due to increased

secretion, and not merely to *expulsion*, because the gall-bladder had been wellnigh emptied by compression, and the cystic duct had been clamped: moreover, the increased flow was far too prolonged in some of the experiments to be attributable to spasm of the larger bile-ducts; therefore, an increase in secretion must have been the cause. 2. When the bile is prevented from entering the intestine, podophylline acts less powerfully and less quickly than when bile is introduced. 3. Augmentation of the biliary secretion is most marked when the purgative effect is not severe; indeed, if the purgative effect be very decided (*Experiment* 9), diminution and not augmentation of the biliary secretion may be the chief result. 4. Podophylline purgation is apparently due to a local action, for the irritation of the intestinal mucous membrane extends gradually from above downwards. 5. The bile secreted under the influence of podophylline, although it may be in increased quantity, contains as much of the special biliary matter as bile secreted under normal conditions.

These results are in exact accordance with clinical experience of the action of podophylline in man, but in addition they show that this substance actually increases the *secretion* of biliary matter, and that the liver is stimulated to secrete bile of the normal composition. They therefore supply information of a precise and important character, which the observations on the human subject have failed to give.

In the experiments with podophylline, performed by Hughes Bennett's committee above referred to, it was found that podophylline *diminishes* the secretion of bile. How is that statement to be reconciled with the above? The principal explanation is probably this, that in the experiments of the committee the doses given were large and generally produced *profuse purgation*. We see that in experiment 9 of this series diminished bile-secretion was the chief result of a dose that was too large, and it may be repeatedly observed in the following experiments. 1. That when a substance produces purgation, but does not stimulate the liver, it diminishes the secretion of bile. 2. That when a substance stimulates the liver as well as the intestinal glands, a moderate dose increases both the hepatic and the intestinal secretion, the effect on the former being

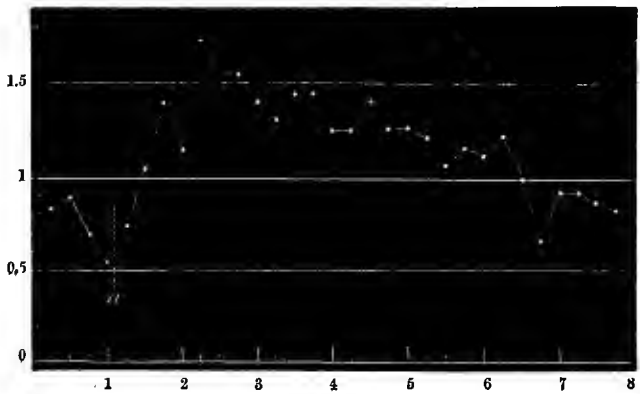
most marked in the earlier part of the experiment, and diminishing as the purgative effect increases; but an excessive dose, by producing a violent purgative effect early in the experiment, may occasion nothing but diminished secretion of bile.

Action of Aloes.

Although aloes has been found by Röhrig to accelerate the biliary secretion, we were anxious to compare its action, as ascertained by our method, with that of other substances; and we also desired to know the composition of the bile secreted before and after its administration.

Experiment 11. Dog that had fasted 18 hours, weight 8.6 kilogrammes.—Sixty grains of aqueous extract of Socotrine aloes in 12 cc. of water were injected into the duodenum (*a*, Fig. 11)[1]. A decided increase in the biliary secretion was perceptible within half-an-hour thereafter. After attaining a maximum about an hour and a half after the administration of

Fig. 11.



Secretion of bile before and after sixty grains extract of Socotrine aloes in 12 cc. water were injected into the duodenum at *a*.

[1] This dose was probably much larger than need have been given, but when these earlier experiments were performed, we were under the impression that the dog requires larger doses than man. Further experience convinced us that this is exceptional. In many subsequent experiments we found that doses of various substances similar to those given to man act on the hepatic and intestinal glands of the dog.

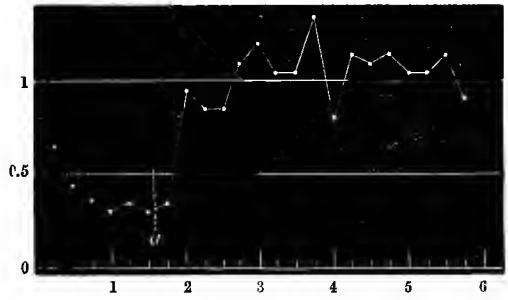
the drug, the secretion gradually fell; but although the experiment was continued for seven hours after the aloes was given, the effect had not disappeared.

AUTOPSY.—The aloes had extended along two-thirds of the small intestine, which contained about an ounce and a half of viscous fluid as the only evidence of purgation. There was a decided increase in the vascularity of the mucous membrane in this part of the intestine. The stomach contained a little mucus. Its mucous membrane was pale.

Experiment 12. Dog that had fasted 18 hours. Weight 5 kilogrammes.—Sixty grains of extract of Socotrine aloes in 12 cc. water were injected into the duodenum (at *a* Fig. 12). As in the previous experiment, the biliary secretion was increased within half an hour, and it became very strongly marked.

AUTOPSY.—The aloes had extended half way down the small intestine. This portion of the intestine contained about two ounces of viscous fluid; and its mucous membrane, together with that of the stomach, was intensely red.

Fig. 12.



Secretion of bile before and after sixty grains extract of Socotrine aloes in 12 cc. water were injected into the duodenum at *a*.

Composition of the Bile before and after Aloes.

It is evident from Tables IV. and V. that, under the influence of aloes, the bile became more watery; nevertheless, the amount of bile-solids secreted per unit of time increased.

TABLE IV.—*Aloes.*

Experiment 11.	Before.	After.
Water	84.11	91.44
Bile-acids, pigments, cholesterine, fats	12.45	7.53
Mucus	1.77	0.38
Ash	1.67	0.65
	100.00	100.00
Velocity of secretion per half-hour	1.5 cc.	2.65 cc.

TABLE V.—*Aloes.*

Experiment 12.	Before.	After.
Water	83.93	86.75
Bile-acids, pigments, cholesterine, fat	12.30	10.79
Mucus	2.74	1.49
Ash	1.03	0.97
	100.00	100.00
Velocity of secretion per half-hour	0.66 cc.	2.2 cc.

Results of Experiments with Aloes.—1. Sixty grains of the extract of Socotrine aloes, when placed in the duodenum, powerfully stimulated the liver. 2. Under its influence the liver excreted a greater quantity of biliary matter in a given time, although the bile was rendered more watery. 3. Coincident with the marked action on the liver there was only slight purgation.

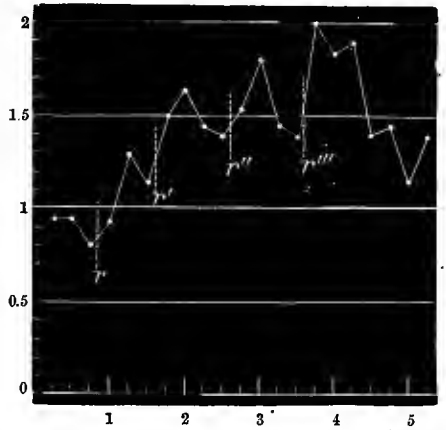
ACTION OF RHUBARB.

The following experiments show that rhubarb is also an undoubted hepatic stimulant. The ordinary infusion of the *British Pharmacopœia* was made with Indian rhubarb; it was then filtered and concentrated until 5 cc. contained the active part of seventeen grains of rhubarb. This was the dose employed.

Experiment 13. Dog that had fasted 15 hours. Weight 22·2 kilogrammes.—5 cc. of the above infusion of rhubarb were injected into the duodenum four times in succession

(r, r', r'', r''', Fig. 13). Within half-an-hour after every dose there was an increase in the biliary secretion.

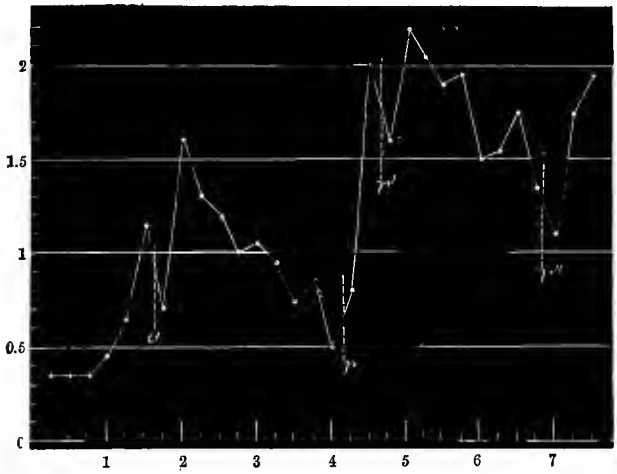
Fig. 13.



Secretion of bile before and after 5 cc. of a concentrated infusion of rhubarb were injected into duodenum at r, r', r'', r'''.

AUTOPSY.—The rhubarb had extended along about a third of the small intestine. There was no unusual redness of the

Fig. 14.



Secretion of bile before and after rhubarb. Artificial respiration improved at a. 5 cc. concentrated infusion of rhubarb injected into duodenum at r, r', and r''.

mucous membrane, and there was only slight evidence of purgative action.

Experiment 14. Dog that had fasted 18 hours. Weight 13.4 kilogrammes.—The artificial respiration, which was deficient at the commencement of this experiment, was improved at *a*, Fig. 14. This was followed by an increase in the secretion of short duration: 5 cc. of the same infusion of rhubarb as that used in the previous experiment were injected into the duodenum three times in succession (*r*, *r'*, *r''*, Fig. 14). The biliary secretion was augmented within half-an-hour after each injection.

AUTOPSY.—The rhubarb had extended along four-fifths of

Experiment 11.		Experiment 12.		Experiment 13.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
0.85		0.65		1.15	
0.9	0.348	0.42		0.95	0.173
0.7		0.37		0.95	
0.55		0.3	0.264	0.80	
a		0.35		*r*	
0.75		0.3		0.95	
1.05		*a*		1.3	
1.4		0.35		1.15	
1.15		0.97		*r'*	
1.75	0.697	0.87		1.5	
1.55		0.85		1.65	0.27
1.55		1.1		1.45	
1.4		1.2		1.4	
1.3		1.05	0.93	*r''*	
1.45		1.05		1.55	
1.45		1.35		1.8	0.279
1.25		0.8		1.45	
1.25		1.15		1.4	
1.4		1.1		*r'''*	
1.25		1.15		2.0	
1.25		1.05		1.85	0.322
1.2		1.05		1.9	
1.05		1.15		1.4	
1.15		0.9		1.45	
1.1				1.15	
1.2				1,4	
1.0					
0.65					
0.9					
0.9					
0.85					
0.8					

the small intestine. There was no unusual redness of the mucous membrane. The portion of intestine through which the rhubarb had extended contained 120 cc. of a thick yellowish fluid: there was, therefore, decided evidence of purgative action.

The amount of water given with the rhubarb in these experiments was so trivial that it may be entirely disregarded.

Composition of the Bile before and after Rhubarb.

TABLE VI.—*Rhubarb.*

Experiment 13.	Before.	After the second dose.	At the close of the experiment.
Water	88.80	89.28	88.98
Bile-acids, pigments, cholesterine, fat	9.60	9.60	9.60
Mucus	1.00	0.60	0.80
Ash	0.60	0.52	0.62
	100.00	100.00	100.00
Velocity of secretion per half-hour	1.9 cc.	2.95 cc.	2.55 cc.

TABLE VII.—*Rhubarb.*

Experiment 14.	Before.	After.
Water	85.47	86.23
Bile acids, pigments, cholesterine, fat	11.59	11.03
Mucus	1.87	1.72
Ash	1.07	1.02
	100.00	100.00
Velocity of secretion per half-hour	1.45 cc.	3.95 cc.

It therefore appears that rhubarb, like podophylline, excites the liver to secrete bile, having a composition similar to that secreted under normal conditions.

Results of Experiments with Rhubarb.—1. An infusion of seventeen grains of Indian rhubarb, when placed in the duodenum, never failed to increase the secretion of bile within half-an-hour after it was given. 2. The bile, although secreted in increased quantity, had the composition of normal bile as

regards the biliary constituents proper. 3. The doses which excited the liver had in one case no marked purgative effect, but in another case the purgative effect was considerable.

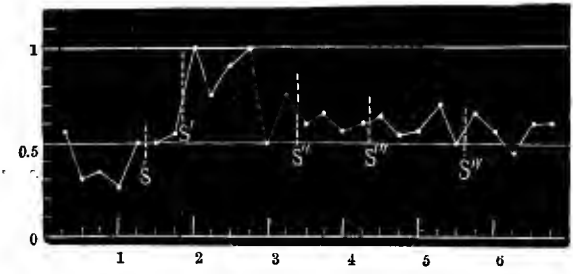
Notwithstanding the fact that rhubarb has been given to man for an indefinitely long period, there has always been considerable doubt as to its being a cholagogue, possibly because the colouring matter of the rhubarb increases the colour of the dejections in a manner similar to an increased discharge of bile. But by this method of investigation this source of fallacy is eliminated, and the action of rhubarb as a cholagogue proved in the case of the dog, and there seems no longer any reason to doubt that it has a similar action in man. If the amount of bile secreted per kilogramme of dog under the influence of rhubarb be compared with the results of the action of podophylline, it will be seen that rhubarb is a less powerful cholagogue; a conclusion that is quite in accordance with observations on man.

Action of Senna.

Senna excites the liver, but not so powerfully as rhubarb. The ordinary infusion of senna of the *British Pharmacopœia* was prepared and concentrated until 5 cc. contained the active part of forty-five grains of senna; a small dose for a man.

Experiment 15. Dog that had fasted 19 hours. Weight 8 kilogrammes.—5 cc. of the above-mentioned concentrated infusion of senna were injected into the duodenum five times in succession (s, s', s'', s''', s^{iv}, Fig. 15). The secretion of bile

Fig. 15.



Secretion of bile before and after senna. 5 cc. concentrated infusion of senna injected into duodenum at s, s', s'', s''', s^{iv}.

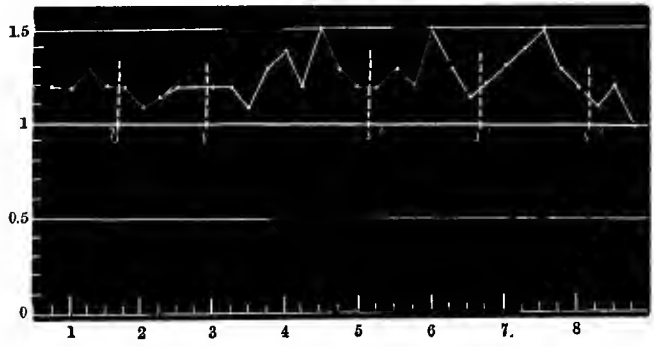
rose rapidly after the second dose, as in the previous experiment, but it soon fell again; and the third, fourth, and fifth doses did not increase it.

AUTOPSY.—The senna had extended along three-fourths of the small intestine, which contained 80 cc. of liquid. Seeing that the amount of fluid injected was 25 cc., considerable purgation had been produced. There was a considerable increase in the vascularity of the duodenal mucous membrane, but elsewhere there was no unusual redness.

Experiment 16.—Dog that had fasted 18 hours. Weight 23.1 kilogrammes.—½ cc. bile and 5 cc. water injected into duodenum at *e* (Fig. 16) and ½ cc. bile with 5 cc. infusion of senna of the strength above mentioned were injected at *s*, *s'*, *s''*, *s'''*. There was only a slight increase in the biliary secretion.

AUTOPSY.—The senna had passed through the whole length of the small and had entered the large intestine. The amount of fluid in the small intestine was 103 cc., showing that a very considerable purgative effect had been produced.

Fig. 16.



Secretion of bile before and after senna. ½ cc. bile and 5 cc. water injected. ½ cc. bile and 5 cc. concentrated infusion of senna injected into duodenum at *s*, *s'*, *s''*, and *s'''*.

It appears from this analysis and from the velocity of secretion, that although senna causes the liver to excrete more biliary matter, its power is below that of rhubarb, as may be further seen by comparing the amount of bile secreted per

kilogramme of dog, under the influence of senna and of rhubarb. It is extremely probable that the greater purgative influence of senna as compared with rhubarb is one cause of its less powerful action as a cholagogue (see p. 21).

Experiment 14.		Experiment 15.		Experiment 16.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.	cc.	cc.
0.37		0.55		1.2	
0.37		0.30		1.2	0.212
0.35		0.35	0.175	1.3	
0.45		0.25		1.2	
0.65		0.5		*e* ——	
1.15		*s* ——		1.2	
0.7		0.5		1.1	
1.6		0.55		1.15	
1.3		*s′* ——		1.2	
1.2		1.0		1.2	
1.0		0.75	0.456	*s* ——	
1.05		0.9		1.2	
0.95		1.0		1.2	
0.75	0.227	0.5		1.1	
0.85		0.75		1.3	
0.5		*s″* ——		1.4	
r ——		0.6		1.2	
0.8		0.65		1.5	
2.0		0.55		1.3	
r′ ——		0.6		1.2	
1.6		*s‴* ——		*s′* ——	
2.2		0.62		1.2	
2.05	0.604	0.52	0.298	1.3	
1.9		0.55		1.2	
1.95		0.7		1.5	
1.5		0.5		1.3	
1.55		*s*iv ——		1.17	
1.72		0.67		*s″* ——	
1.37		0.55		1.2	
r″ ——		0.45		1.3	
1.1		0.6		1.4	0.238
1.75		0.6		1.5	
1.97				1.3	
				1.2	
				s‴ ——	
				1.1	
				1.2	
				1.0	

TABLE VIII.—*Senna.*

Experiment 15.	Before.	After.
Water	90.63	91.31
Bile-acids, pigments, cholesterine, fat	7.20	6.75
Mucus	1.30	1.20
Ash	0.87	0.74
	100.00	100.00
Velocity of secretion per half-hour	0.82 cc.	1.136 cc.

Results of the Experiments with Senna.—1. Senna is a hepatic stimulant of feeble power. 2. It renders the bile more watery.

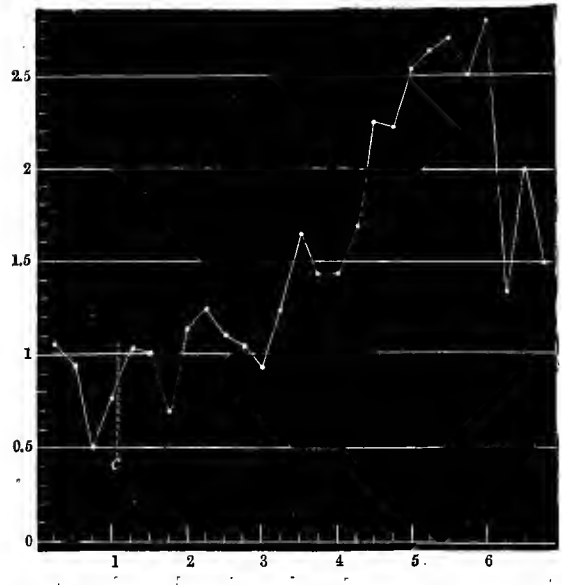
ACTION OF COLCHICUM.

Colchicum has been recommended as a cholagogue in cases of gout, but its action on the liver has not hitherto been tested by direct experiment.

Experiment 17. Dog that had fasted 16 hours. Weight 23.5 kilogrammes.—Sixty grains of the aqueous extract of colchicum of the *British Pharmacopœia* in 10 cc. of water were injected into the duodenum (*c*, Fig. 17). In an hour the biliary secretion began to increase, and five hours after the injection it was nearly five times more than before the drug was given. The secretion then fell, and just at the close of the experiment a large quantity of liquid fæces was discharged. The rise in the curve in Fig. 17 suggests a very powerful stimulation of the liver, but it must be remembered that the animal was of large size, and the table of numbers shows that the secretion per kilogramme of dog never went higher than 0.453 cc.

AUTOPSY.—There was great vascularity of the upper four-fifths of the mucous membrane of the small intestine. The vascularity of the duodenum was intense. The mucous membrane of the large intestine was also unusually vascular. The gastric mucous membrane was pale. There was evidence of considerable hydrocatharsis in the small intestine. The large intestine was empty, owing to the recent discharge of fæcal matter.

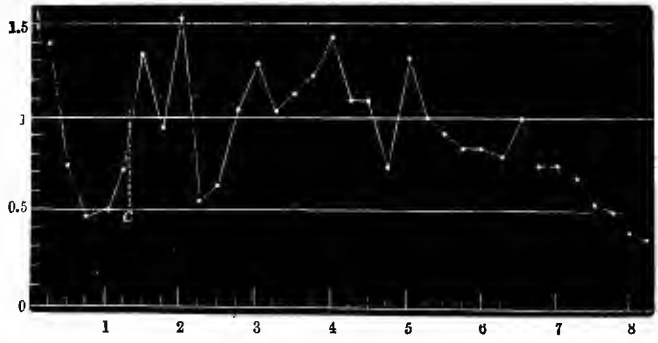
Fig. 17.



Secretion of bile before and after sixty grains extract of colchicum in 10 cc. water were injected into the duodenum at c.

Experiment 18.—Dog that had fasted 18 hours. Weight 23.6 kilogrammes.—Sixty grains of aqueous extract of colchicum in 10 cc. of water were injected into the duodenum (*c*, Fig. 18). Although the biliary flow thereafter varied much, a decided

Fig. 18.



Secretion of bile before and after sixty grains of aqueous extract of colchicum in 10 cc. of water were injected into duodenum at c.

increase was evident an hour and a half after the administration of the drug. The increase lasted about four hours, after which the secretion gradually fell. The liver was certainly excited, but not powerfully, for the secretion of bile per kilogramme of dog did not rise above 0.205 cc.

AUTOPSY.—There was increased vascularity of the mucous membrane of the upper three-fourths of the small intestine. The whole small intestine contained evidence of powerful cathartic action.

Experiment 17.		Experiment 18.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	cc.	cc.	cc.
1.07		1.42	
0.92	0.138	0.75	
0.5		0.47	0.1
0.77		0.5	
c		0.72	
1.02		c	
1.0	0.207	1.35	
0.7		0.95	0.186
1.15		1.55	
1.25		0.55	
1.1	0.227	0.62	
1.05		1.02	
0.95		1.3	
1.25		1.02	
1.65	0.216	1.15	0.205
1.45		1.22	
1.45		1.47	
1.7		1.1	
2.25	0.371	1.1	
2.22		0.75	
2.55		1.35	
2.65		1.0	
2.7	0.453	0.95	
2.5		0.85	
2.8		0.85	
1.36		0.8	
2.0		1.0	
1.5		0.75	
		0.75	
		0.7	
		0.55	
		0.5	
		0.4	
		0.37	

These experiments show that the aqueous extract of colchicum in large doses increases the biliary secretion.

TABLE IX.—*Composition of the Bile before and after Colchicum.*

Experiment 18.	Before.	After.
Water	88.434	90.63
Organic Bile-solids	10.616	8.75
Ash	0.950	0.62
	100.00	100.00
Velocity of bile-secretion per half-hour	1.2 cc.	2.24 cc.

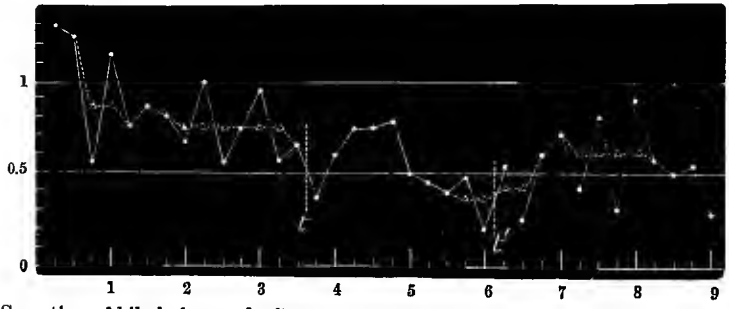
It appears from the above analysis that colchicum rendered the bile more watery; nevertheless, owing to the increased velocity of secretion, more biliary matter is excreted by the liver under under its influence.

Results of Experiments with Colchicum.—1. Sixty grains of the aqueous extract of colchicum powerfully excited the liver, and produced hydrocatharsis, although the absolute amount of bile secreted per kilogramme of dog was never very high. 2. Colchicum, although it increases the amount of biliary matter excreted by the liver, renders the bile more watery.

ACTION OF TARAXACUM.

Experiment 19. Middle-sized dog that had fasted 24 hours. —One hundred and eighty grains of solid extract of taraxacum in 25 cc. of water were injected into the duodenum (*t*, Fig. 19);

Fig. 19.



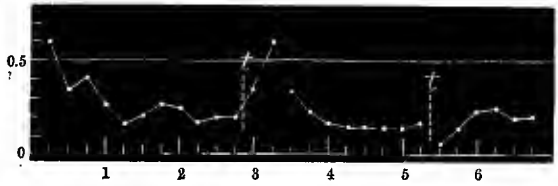
Secretion of bile before and after taraxacum. *t*, 180 grains; *t'*, 120 grains of solid extract of taraxacum in 25 cc. of water were injected into the duodenum. (The triangles and dotted lines indicate the *mean* of the high and low readings in order that a conclusion regarding the effect of the substance may be more easily arrived at.)

and two hours after this, one hundred and twenty grains in the same quantity of water were injected (*t'*). After both doses there was a greater increase in the biliary secretion than was at all likely to have been caused by the same quantity of water. (See *Experiment* 6.)

AUTOPSY.—The taraxacum had passed along nearly the whole length of the small intestine. Most of the fluid had been absorbed. There was no evidence of purgative action.

Experiment 20. Small dog that had fasted 18 hours.—One hundred and twenty grains of solid extract of taraxacum in 15 cc. of water were injected into the duodenum (*t*, Fig. 20), and this dose was repeated in two-and-a-half hours. The increase of the biliary secretion after the second dose was trivial; but after the first it was considerable, though of short duration. An examination of the intestine at death revealed no purgative action.

Fig. 20.



Secretion of bile before and after taraxacum. 120 grains of solid extract of taraxacum in 15 cc. of water injected into the duodenum at *t* and *t'*.

From these experiments it may be concluded that taraxacum is a very feeble hepatic stimulant, a conclusion that is in harmony with clinical experience, although the observations on man—from the nature of the case—have yielded nothing perfectly definite. We think it unnecessary to detail these two experiments more fully.

ACTION OF SCAMMONY.

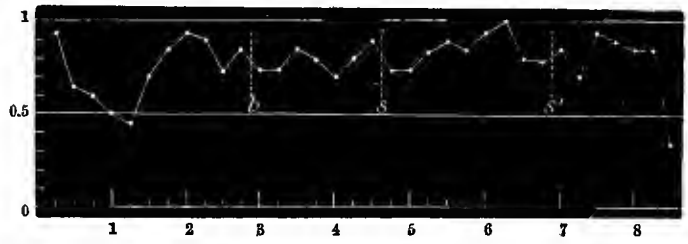
The resin of scammony, being insoluble in water, was dissolved in dilute alcohol, and some bile was added, in order still further to promote its absorption from the alimentary canal.

Experiment 21. Dog that had fasted 18 hours. Weight 9.5 kilogrammes.—2.5 cc. bile were injected into the duodenum

(*b*, Fig. 28). This produced no notable effect. Twenty grains of scammony resin were dissolved in 3.5 cc. rectified spirit, 3 cc. water and 3 cc. bile were then injected (*s*), and this dose was afterwards repeated (*s'*). There was a slight increase in the biliary secretion.

AUTOPSY.—There was greatly increased vascularity of the mucous membrane of the whole length of the small intestine. Vascularity of the gastric mucous membrane was also somewhat increased. There was evidence of severe purgative action in the whole extent of both the small and large intestine.

Fig. 21.

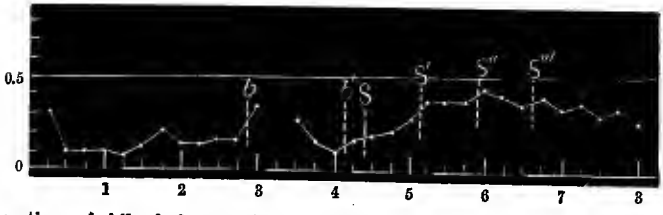


Secretion of bile before and after scammony. Bile injected into duodenum at *b*, and scammony with bile and alcohol at *s* and *s'*. (See text.)

Experiment 22. Dog that had fasted 19 hours. Weight 6.8 kilogrammes.—In this experiment it was determined to give scammony in smaller doses; 1 cc. bile and 2 cc. water were injected into the duodenum at *b*, Fig. 22.

The exact effect of this was not ascertained, owing to the loss of the bile secreted during one of the periods. About an hour after this, 0.25 cc. bile, 0.5 cc. rectified spirit, and 1.25 cc. water, were injected (*b'*). This having scarcely any effect, it was given with four grains of scammony resin at *s*, and again

Fig. 22.



Secretion of bile before and after scammony. Bile given at *b* and *b'*; scammony, etc., given at *s*, *s'*, *s''*, *s'''*.

at s'. The amount of scammony was doubled, and this dose was given at s'' and s'''. There was an increase of the biliary secretion after the first two doses of scammony, but after the third and fourth the secretion diminished.

As two experiments, not here reported, in which alcohol only was given, proved that it certainly does not augment the biliary secretion, this experiment shows that scammony is a hepatic stimulant, although not a powerful one.

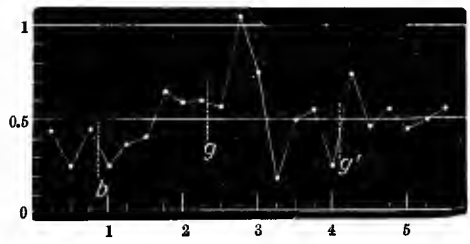
AUTOPSY.—The scammony had passed along two-thirds of the small intestine. There was decided evidence of purgation, but no remarkable increase in the vascularity of the mucous membrane.

From these experiments it appears that scammony is a cholagogue of feeble power, and it seems unnecessary to detail them further.

ACTION OF GAMBOGE.

Experiment 23. Dog that had fasted 18 hours. Weight 4.8 kilogrammes.—3 cc. of bile and 3 cc. of water were injected into the duodenum at *b* (Fig. 23). Previously to this there was, considering the small size of the dog, a large secretion of bile. The increased secretion which followed the injection was probably owing to the action of the bile. Twenty grains of gamboge in the same quantity of bile and water were given at

Fig. 23.



Secretion of bile before and after gamboge. 3 cc. bile and 3 cc. water injected into duodenum at *b*; twenty grains gamboge at *g*, and forty grains at *g'*, in the same fluid injected into duodenum.

g, and forty grains in the same fluid at *g'*. Half an hour after the first dose there was a decided acceleration of the biliary

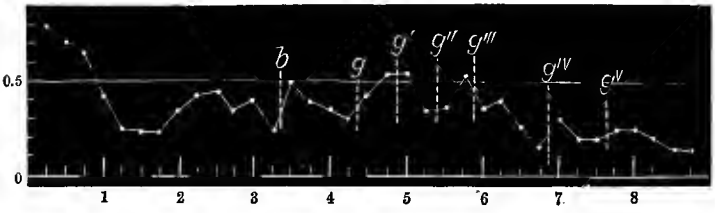
flow, but in an hour afterwards it had temporarily sunk nearly to zero. If the mean be taken, it will be found that the increase of secretion was so slight that it might have been due to the bile that was given with the gamboge. On the whole, therefore, it can scarcely be said that the amount of bile secreted was increased by the gamboge, and certainly the next experiment lent no support to such a view of the matter.

AUTOPSY.—There was great redness of the mucous membrane in the upper half of the small intestine. There was evidence of profuse hydrocatharsis in this portion of the gut. Some of the gamboge had passed into the stomach, the mucous membrane of which was somewhat reddened.

Experiment 24. Dog that had fasted 19 hours. Weight 8 kilogrammes.—1 cc. of bile and 2 cc. of water were injected into the duodenum at *b* (Fig. 24); four grains of gamboge in 0.2 cc. of bile and 2 cc. of water were injected at *g*, *g'*, and *g''*. At *g'''*, g^{iv}, g^{v}, twice the amount of gamboge was given in the same fluid. The increase in the bile-secretion after the first dose was trifling. The chief result of the experiment was *diminution* of the secretion.

AUTOPSY.—There was profuse hydrocatharsis in the small intestine. There was no very noteworthy increase in the vascularity of the mucous membrane.

Fig. 24.



Secretion of bile before and after gamboge. (See text.)

In Experiment 24, a smaller quantity of bile was given than in Experiment 23, in order to eliminate, as far as possible, its stimulating effect on the liver: 24 is therefore a better experiment than 23, and it affords no sufficient evidence that gamboge is a hepatic stimulant. It is thought unnecessary to detail the experiments on gamboge further. It is, however,

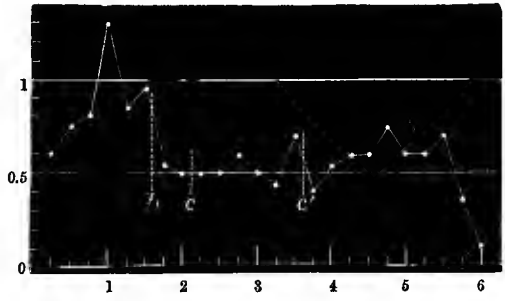
extremely interesting to contrast the negative effect on the liver of this hydrocathartic with the positive effect of colchicum, also a hydrocathartic. In both there was violent irritation of the mucous membrane of the duodenum and small intestine generally. And it is important to observe that in the case of gamboge this irritation gave rise to no increased action of the liver, showing that duodenal irritation is not of necessity followed by hepatic excitement.

Action of Castor-Oil.

Röhrig found that castor-oil has scarcely any effect on the hepatic secretion. It appeared, however, desirable to emulsify the oil with bile, so that its condition in the intestine might more closely resemble that in any normal case.

Experiment 25. Dog that has fasted 18 hours. Weight 7.7 kilogrammes.—3 cc. of bile were injected into the duodenum at *b* (Fig. 25). One ounce of castor-oil, emulsified with 3 cc. of bile, was injected into the duodenum at *c*, and again at *c'*. A slight increase in the bile-secretion followed the second dose; but as its extent was trifling, it should probably be disregarded. There was a great diminution towards the close of the experiment.

Fig. 25.



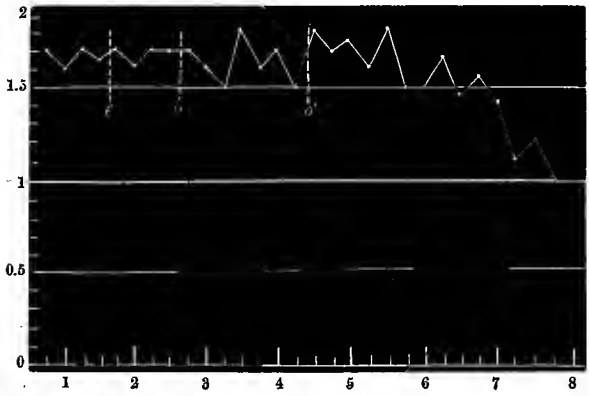
Secretion of bile before and after castor-oil. 3 cc. of bile injected into the duodenum at *b*. The same, with one ounce of castor-oil, given at *c*, and at *c'*.

Autopsy.—There was decided evidence of purgation in the small intestine. There was no unusual redness of the mucous membrane, save at the lower part of the duodenum.

Experiment 26. Dog that had fasted 18 hours. Weight 24.5 kilogrammes.—3 cc. bile injected into the duodenum at *b*, (Fig. 26), and 28.5 cc. castor-oil with 3 cc. bile injected at *o*, and again at *o'*.

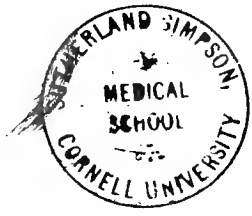
AUTOPSY.—The oil had extended throughout the whole length of the small and large intestine. There was evidence of profuse purgative action, but the increased vascularity of the intestinal mucous membrane was slight.

Fig. 26.



Secretion of bile before and after castor-oil. 3 cc. bile injected into duodenum at *b*. The same with 28.5 cc. castor-oil injected at *o*, and again at *o'*.

Experiment 25 and 26 show the effect of an agent on the biliary secretion that does not excite the liver, but produces purgation by a mild irritation of the intestine. It is evident in both cases that the biliary secretion was decidedly diminished when the purgative effect became strongly marked, thus showing that purgation *per se* does nothing else than diminish the secretion of bile.



EXPERIMENTS ON THE BILIARY SECRETION OF THE DOG. By Prof. RUTHERFORD and M. VIGNAL.

SECOND SERIES.

IN the first series of our experiments we gave an account (this *Journal*, x. 253) of the action of podophyllin, colchicum, rhubarb, aloes, scammony, taraxacum, senna, gamboge, croton and castor-oil on the secretion of bile in the dog. We have now to detail the actions of a number of other substances. In these experiments we have adopted precisely the same method as in the previous ones; that is to say, we have always used dogs; these being the only animals suitable for the purpose. They had always a full meal of flesh at four o'clock in the afternoon, and the experiment was begun at nine o'clock on the following morning, so that digestion and absorption had fully taken place;—a condition that is essential for obtaining a constant secretion of bile. In all cases, irregular muscular movements were prevented by small doses of curara, it having been ascertained that these have no apparent influence on the biliary secretion, nor do they prevent the manifestation of the effects of hepatic stimulants. In consequence of the curara paralysis respiration was of course maintained artificially. As before, a glass cannula was tied in the common bile-duct, the cystic duct was clamped, and all the bile secreted was thereby compelled to flow out through the cannula into a finely graduated cc. measure, where it was constantly collected and the amount observed and recorded every fifteen minutes. Each experiment usually lasted an entire day, at the close of which the animal was killed, and the alimentary canal examined. The various substances were always injected directly into the duodenum, for the reason that, in fasting dogs, the stomach is apt to contain a large quantity of mucus that seriously interferes with the certainty of the speedy absorption of the various substances administered. We therefore had recourse to the small intestine, and we preferred the duodenal portion,

in order that we might certainly bring the substance into contact with *its* mucous membrane, in case of any sympathy between it and the liver. The whole method is more fully detailed in our previous communication, but it may be well to state that in these experiments anæsthetics were not administered, because of their disturbing influence on the biliary secretion. In two of our earlier experiments we administered chloroform during the preliminary operation, but the stimulation of the liver produced thereby was so remarkable, that the animals were rendered useless for further experimentation. To avoid equivocal results, we therefore abstained from the preliminary administration of any substance other than curara.

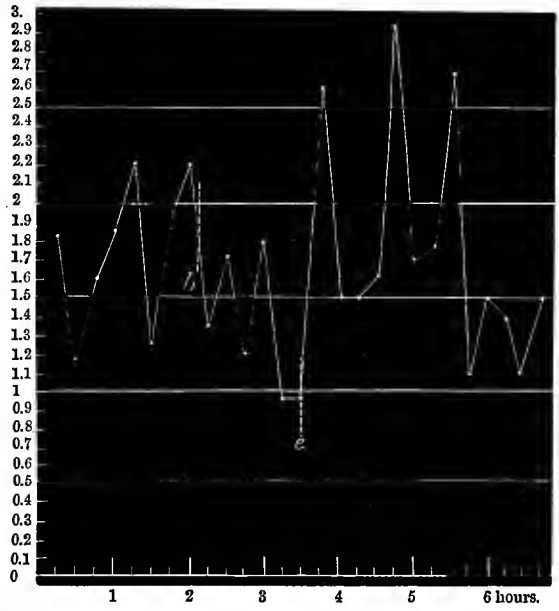
We have still confined our attention to the physiological actions of cholagogues, for it cannot be doubted that the thorough investigation of this subject is of great importance for the advance of scientific medicine.

Action of "Euonymin."

Wood and Bache in the *United States Dispensatory* for 1869 (p. 374) state that "the precise virtues of the bark of Euonymus atropurpureus have not been determined." Mr C. A. Santos—quoted by them—describes it as "tonic, hydragogue cathartic, diuretic, and antiperiodic." Dr Tidyman informed them that he had obtained useful effects from it, as an alterative of the hepatic function. Wood and Bache conclude that "on the whole its character is somewhat uncertain; and it might well form a subject of further examination." The American "Eclectics" give "Euonymin" as a mild aperient in doses of from one to two grains. The substance used by them however is a very complex substance, only a portion of which consists of the active principle—the *true* euonymin. Mr Clothier found it to produce active purgation without griping. The substance employed in our experiments is an impure resin prepared by precipitating the tincture of euonymin with water acidulated with hydrochloric acid. It was obtained from Messrs Tilden and Co. of New York.

Experiment 27. Dog that had fasted 17 hours. Weight 19 kilogrammes. (Fig. 27.)

Fig. 27.



Secretion of bile before and after "euonymin." 2 cc. bile and 2 cc. water injected into duodenum at *b*. 5 grains of "euonymin," together with the above fluid, injected at *e*.

The irregularity in the biliary flow in this case was certainly owing to an irregularity in *secretion*, for the cannula was perfectly patent throughout the whole of the experiment. The irregularity did not consist in the bile being expelled in jets, as might have been expected had it been owing to contraction of the larger bile-ducts at intervals, but there was a rapid and steady flow for some minutes, and then for a while it flowed much more slowly. This irregularity of secretion was probably in large measure due to unusual traction upon the bile-duct and liver during the introduction

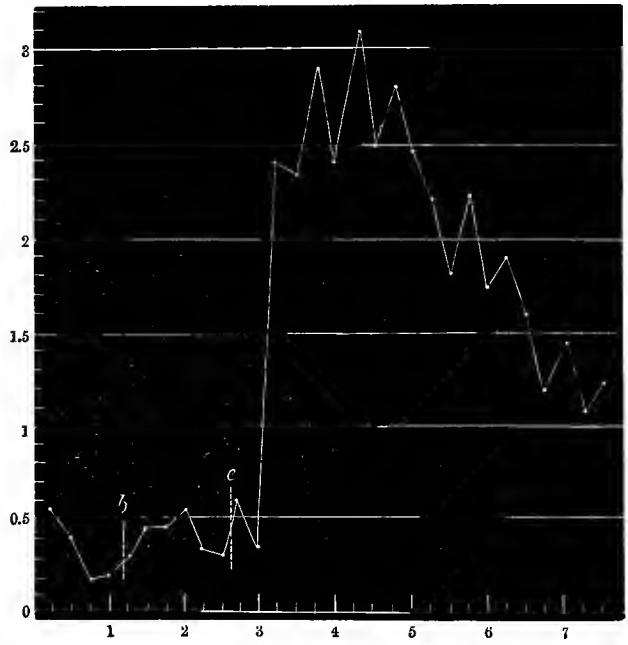
[1] Every dot in the curves in all the figures indicates the amount of bile secreted during the preceding fifteen minutes. The quantity is always expressed in cubic centimetres.

of the cannula, which in this case was much more difficult than usual. We have repeatedly observed that unless this part of the preliminary operation be conducted so as to very slightly disturb the bile-duct and its surroundings, the biliary secretion is rendered irregular. Nevertheless it is evident that in this case the "euonymin" stimulated the liver.

AUTOPSY.—There was very slight evidence of purgative action, but the mucous membrane of the upper fourth of the small intestine was much more vascular than usual.

Experiment 28. Dog that had fasted 24 hours. Weight 23.3 kilogrammes. (Fig. 28.)—The unusually long fast resulted from the animal having refused to take food on the afternoon of the day preceding the experiment. It was probably owing to this circumstance that the secretion of bile was so low at the beginning of the experiment.

Fig. 28.



Secretion of bile before and after "euonymin." 1.1 cc. bile and 3 cc. water injected into the duodenum at *b*. The same with 5 grains "euonymin" injected at *e*.

AUTOPSY.—Stomach contracted, mucous membrane normal. The "euonymin" had extended along about a third of the small intestine. The mucous membrane of the upper third was extremely vascular. Mucous flakes were scattered over the surface, and the whole appearance of the membrane reminded us of the effects of podophyllin. But notwithstanding the very obvious irritation, the intestine at this part contained only a small quantity of a watery fluid. The remainder of the intestine was dry and contracted, without any signs of irritation.

Results of Experiments with "Euonymin."—1. Five grains of "euonymin," when mixed with a small quantity of boiling water and placed in the duodenum, powerfully stimulated the liver[1]. 2. Coincident with the marked action of the liver there was only a slight increase of intestinal secretion. Seeing that Mr Clothier (quoted above) found "euonymin" to be an active purgative in the human subject, these experiments suggest that the purgative effect may be chiefly due to increased secretion of bile. At any rate these experiments clearly show that this substance is worthy of receiving far greater attention in practical medicine than it has done hitherto.

ACTION OF "SANGUINARIN."

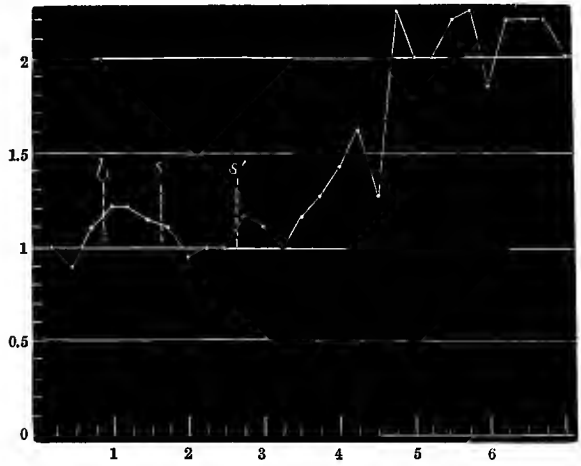
Dr Wood in his excellent *Treatise on Therapeutics* (1874) states (p. 367) that "although Sanguinaria has been used more or less for so many years, we are still without any really definite knowledge of its action. Little or nothing has been added to our knowledge since the papers by Dr Tully in 1830, who stated that when given in small repeated doses it acts as a very decided cholagogue; and more recently it has been affirmed that it is also a stimulating expectorant. In full doses it is certainly a harsh emetic, and in overdoses, according to Tully, it produces with the vomiting burning at the stomach, faintness, vertigo, dimness of vision, general insensibility, coldness, extreme reduction of the force and fre-

[1] The analysis of the bile secreted before and after "euonymin" was lost.

quency of the pulse, great prostration of the muscular strength, and sometimes a convulsive rigidity of the limbs." Dr Wood states that he has never known of its employment except as a stimulant expectorant in obstinate bronchitis. Dr Mothershead of Indianapolis (quoted in Wood and Bache's *United States Dispensatory*, 1869, p. 741) however "speaks in the strongest terms of its efficacy as an excitant of the liver, when given in alterative doses." On the other hand, Prof. Thomas, of Philadelphia (quoted by Wood and Bache, *lib. cit.*, p. 742), found the active principle sanguinarina to "have no effect of any kind directly on the liver" of man. "Sanguinarin" is however recommended by the American "Eclectics" in doses of $\frac{1}{4}$—1 grain as a hepatic alterative. The substance employed in the following experiments is a resin prepared in the same manner as euonymin (see p. 42).

Experiment 29. Dog that had fasted 17 hours. Weight 27.7 kilogrammes. (Fig. 29.)

Fig. 29.



Secretion of bile before and after "sanguinarin." 2 cc. bile and 2.5 cc. water injected into the duodenum at *b*. 1 grain "sanguinarin" in the same fluid injected at *s*. 2 grains "sanguinarin" in the same fluid injected at *s'*.

AUTOPSY.—Mucous membrane of upper two-thirds of small intestine was of a clear claret colour, here and there it was marked by brownish patches of a size varying from that of a

sixpence to that of a half-crown. There were 35 cc. of a thick brown fluid in the small intestine. The brown colour was apparently owing to the presence of the "sanguinarin," a substance of a brownish-red colour.

Experiment 27.		Experiment 28.		Experiment 29.	
Secretion of bile per 15".	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15".	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15".	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
1.82		0.55		1.0	
1.2		0.4		0.9	
1.6		0.2		1.1	
1.85		0.21		*b* ——	
2.2		0.3		1.2	0.1678 cc.
1.3		*b* ——		1.2	
1.95		0.45		1.15	
2.2		0.45		*s* ——	
b ——		0.55	0.0708 cc.	1.1	
1.35		0.35		0.95	
1.7		0.3		1.0	
1.2		*e* ——		1.0	
1.8	0.2578 cc.	0.6		*s'* ——	
0.95		0.35		1.15	
0.95		2.4		1.12	
e ——		2.35		1.0	
2.6		2.9		1.15	
1.5		2.4	0.4678 cc.	1.25	
1.5		3.1		1.4	
1.6		2.5		1.6	
2.95		2.8		1.25	
1.7	0.4789 cc.	2.45		2.22	
1.75		2.25		2.0	
2.7		1.75		2.0	0.3039 cc.
1.1		2.25		2.2	
1.5		1.6		2.22	
1.4		1.85		1.85	
1.1		1.6		2.2	
1.5		1.2		2.2	
		1.45		2.2	
		1.1		2.0	
		1.25			

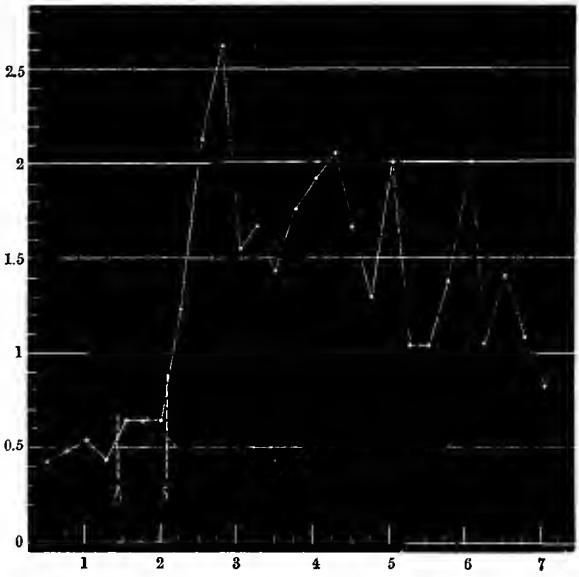
TABLE X.—*Composition of Bile before and after "Sanguinarin."*

Experiment 29.	Before.	After.
Water	90.09	91.41
Bile-acids, pigments, cholesterin, fats ...	7.38	6.57
Mucus	1.04	0.90
Ash	1.49	1.12
	100.00	100.00
Velocity of secretion per half-hour	2.4 cc.	4.25 cc.

It appears from this analysis that under the influence of "sanguinarin" the bile becomes more watery, nevertheless the velocity of secretion having been nearly doubled by this agent, it is evident that the liver secreted more biliary matter.

Experiment 30. Dog that had fasted 17 hours. Weight 20 kilogrammes. (Fig. 30.)

Fig. 30.



Secretion of bile before and after "sanguinarin." 2 cc. bile and 3 cc. water injected into the duodenum at *b*. 1 grain "sanguinarin" in the same fluid injected at *s*.

AUTOPSY.—Vascularity of the mucous membrane of upper half of small intestine somewhat increased. Considerable evidence of purgative action in upper half of small intestine. Contents of a viscid mucous character.

Results of Experiments with "Sanguinarin."—1. In one experiment three grains, in another experiment one grain, of "sanguinarin" when mixed with a small quantity of bile and water and placed in the duodenum powerfully stimulated the

liver. 2. It rendered the bile more watery, nevertheless it caused the liver to secrete more biliary matter in a given time. 3. The secretion of the intestinal glands was slightly increased by these doses. These results show that the statements of Tully and Mothershead ought not to be treated with indifference and neglect, as they at present appear to be, in practical medicine.

Action of "Iridin."

The root of the Iris Versicolor, or American Blue Flag, is said by Wood and Bache (*lib. cit.* p. 487) to possess cathartic, emetic and diuretic properties. The American "Eclectics" have used, under the name of "iridin" or irisin, an oleo-resin obtained by precipitating a tincture of the root with water and mixing the precipitate with an equal weight of some absorbent powder. The dose of this is 1—5 grains as a purgative. "It is thought to unite cholagogue and diuretic with aperient properties" (Wood and Bache, *loc. cit.*). An anonymous writer in the *Lancet* (August 30, 1872) states that "it is gentler in its action than podophyllin, and more reliable when a slight cholagogue action is required for a lengthened period." This statement however has been generally neglected, and the substance appears to be unknown to most persons.

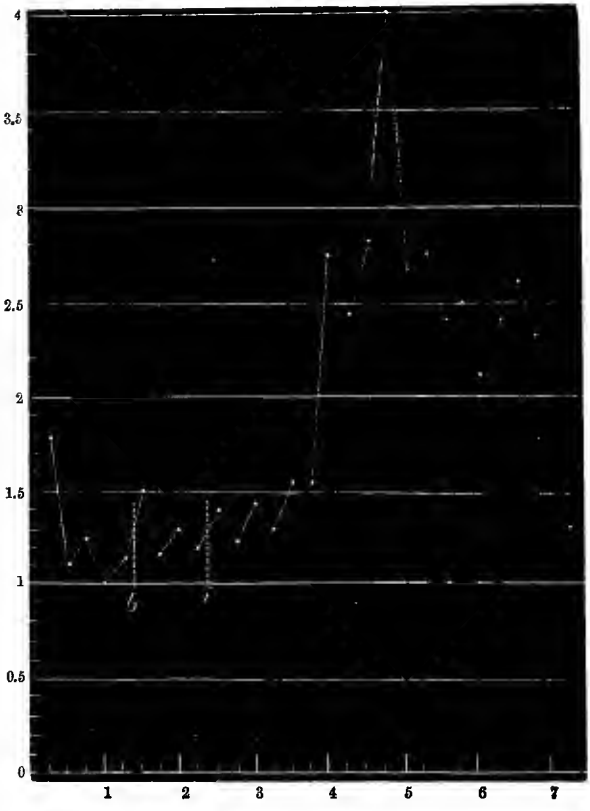
The substance employed by us is a resin prepared in the same way as euonymin (see p. 42).

Experiment 31. Dog that had fasted 17 hours. Weight 22.7 kilogrammes. (Fig. 31.)

Autopsy.—Stomach normal. Mucous membrane of upper two-thirds of small intestine rather more vascular than usual. This portion of the intestine contained 63 cc. of fluid, thus affording evidence of a decided purgative effect.

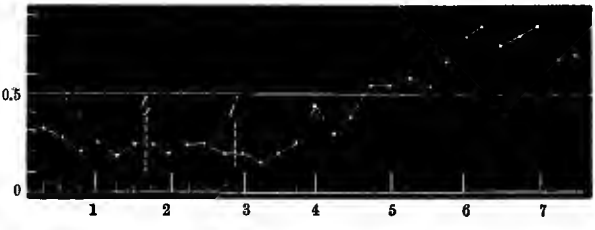
Experiment 32. Dog that had fasted 18 hours. Weight 5.4 kilogrammes. (Fig. 32.)

Fig. 31.



Secretion of bile before and after "iridin." 2 cc. bile and 3 cc. water injected into the duodenum at *b*. 5 grains "iridin" in the same fluid injected at *i*.

Fig. 32.



Secretion of bile before and after "iridin." 2 cc. bile and 2 cc. water injected into the duodenum at *b*. 5 grains "iridin" in the same fluid injected at *i*.

Experiment 30.		Experiment 31.		Experiment 32.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
0.41		1.8		0.32	
0.49		1.1		0.3	
0.52		1.25		0.2	
0.45		1.0		0.25	
b ——		1.15		0.2	
0.65	0.12 cc.	*b* ——		0.25	
0.65		1.5		*b* ——	
0.65		1.16	0.227 cc.	0.25	
s ——		1.3		0.2	
1.25		1.2		0.25	0.166 cc.
2.15		*i* ——		0.25	
2.65	0.401 cc.	1.4		0.2	
1.55		1.25		*i* ——	
1.7		1.45		0.2	
1.45		1.3		0.15	
1.8		1.55		0.2	
1.9		1.55		0.25	
2.02		2.75		0.45	
1.7		2.45		0.3	
1.3		2.8		0.4	
2.0		4.0	0.537 cc.	0.55	
1.05		2.65		0.55	
1.05		2.75		0.6	
1.35		2.4		0.55	
2.0		2.5		0.7	
1.05		2.1		0.85	
1.4		2.4		0.9	
1.1		2.6		0.8	0.638 cc.
0.8		2.3		0.85	
		1.5		0.9	
		1.3		0.7	
				0.75	

AUTOPSY.—Stomach normal. There was increased vascularity of the mucous membrane of nearly the whole length of the small intestine. The redness was not very marked, but it was greater than in the previous experiment. There was decided purgation, the small intestine containing 87 cc. of fluid with abundant mucous flocculi.

Results of Experiments with Iridin.—1. Five grains of iridin when mixed with a little bile and water and placed in the duodenum very powerfully stimulated the liver. It is not so powerful as large doses (four grains) of podophyllin, but it is more powerful than euonymin, as is shown by the

amount of bile secreted per kilogramme of dog; the fractions for the two euonymin experiments being 0.4789 cc. and 0.4678 cc., whereas in the "iridin" experiments they are 0.537 cc. and 0.638 cc. The high fraction in the second iridin experiment probably resulted from a much smaller dog getting the same dose as in the first experiment, the smaller liver being thereby stimulated to do a proportionally greater amount of work[1]. 2. Iridin is also a decided stimulant of the intestinal glands. Judging from these experiments its irritant effects on the intestinal mucous membrane are decidedly less than those of podophyllin, while the purgative effects are greater than in the case of euonymin. The statement of the writer in the *Lancet* (above quoted) that in man "it is gentler in its action than podophyllin" is fully supported by these experiments, and there seems every reason why this substance should be removed from its present obscurity and placed in a prominent position in practical medicine.

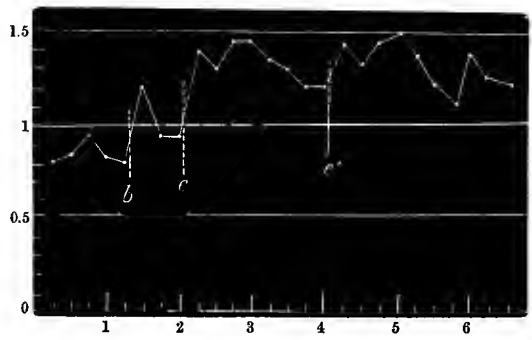
Action of "Leptandria."

"Leptandria" or "Leptandrin" is a resin prepared from the root of the American plant Leptandra Virginica or Veronica Virginica in the same manner as euonymin (see p. 42). It is a remedy that has been much lauded by the "Eclectics" as a cholagogue and tonic. As this remedy is now a good deal employed, it seemed desirable to obtain more precise information regarding its mode of action. The dose for a man is ½—3 grains three or four times daily.

Experiment 33. Dog that had fasted 18 hours. Weight 20.4 kilogrammes. (Fig. 33.)

[1] The analyses of the bile secreted before and after "iridin" were lost.

Fig. 33.



Secretion of bile before and after "leptandria." 3 cc. bile and 3 cc. water injected into the duodenum at *b*. 6 grains "leptandria" in the same fluid injected at *e*. 12 grains "leptandria" in 2 cc. rectified spirit[1] and 8 cc. water injected at *e'*.

TABLE XI.—*Composition of the Bile before and after "Leptandria."*

Experiment 33.	Before.	After.
Water	91.34	91.41
Bile-acids, pigments, cholesterin, fats ...	6.64	6.60
Mucus	0.95	0.92
Ash	1.07	1.07
	100.00	100.00
Velocity of secretion per half-hour	1.9 cc.	2.5 cc.

It appears from this analysis that the bile secreted under the influence of leptandria retained its normal composition.

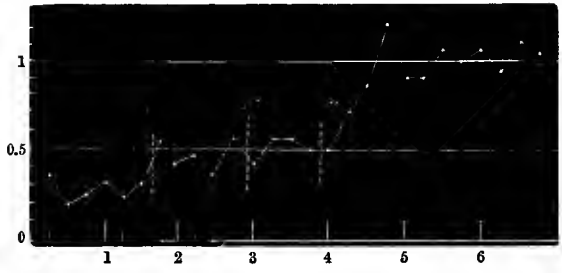
Experiment 34. Dog that had fasted 18 hours. Weight 13.1 kilogrammes. (Fig. 34.)

AUTOPSY.—Slightly increased vascularity of the mucous membrane of the upper half of the small intestine. There was slight purgation;—the upper half of the small intestine containing 37 cc. of a viscous fluid.

Results of Experiments with "Leptandria."—1. "Leptandria" when mixed with bile and placed in the duodenum undoubtedly

[1] We have ascertained that alcohol does not increase the secretion of bile, but rather diminishes it if the dose be large.

Fig. 34.



6 grains "leptandria" in 4 cc. water injected into the duodenum at *e*. 1½ cc. bile and 3 cc. water injected at *e'*. 12 grains "leptandria" in the same fluid injected at *e''*.

stimulates the liver, but its power is very feeble as shown by the small secretion of bile per kilogramme of dog, notwithstanding the large doses given. It excites the liver to secrete bile, having the ordinary composition. Unless the biliary solvent be present, "leptandria" produces scarcely any appreciable effect. In this respect it resembles many other resinous substances, e. g. "podophyllin." 2. It is a feeble stimulant of the intestinal glands.

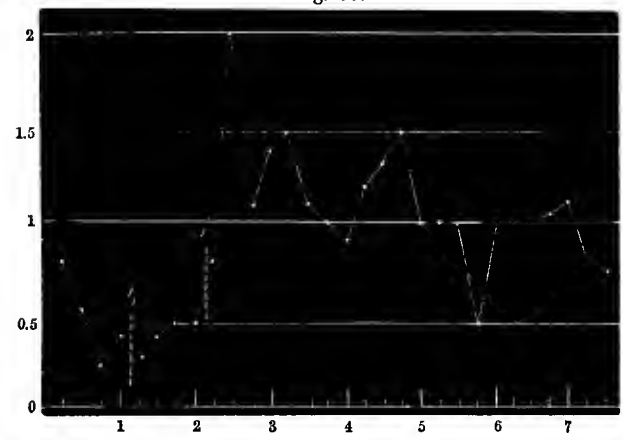
Action of Ipecacuan.

As is well known, ipecacuan is regarded as almost a specific remedy in certain cases of dysentery. It is stated that it gives rise to evacuations containing a large quantity of bile. The manner in which it does this is not definitely known: some maintaining that it permits of biliary discharge by relieving spasm of the bile-ducts. The following experiments, undertaken at the desire of Sir Robert Christison, prove beyond a doubt that this substance is a powerful stimulant of the hepatic secreting apparatus.

Experiment 35. Dog that had fasted 18 hours. Weight 15 kilogrammes. (Fig. 35.)

Autopsy.—The ipecacuan had extended along the upper half of the small intestine, the mucous membrane of which portion was covered with thick white mucus. No purgation.

Fig. 35.

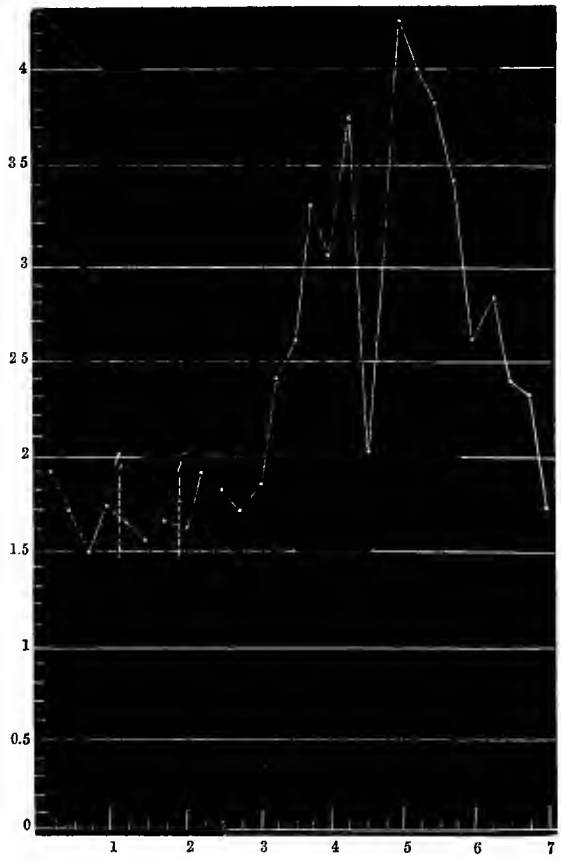


Secretion of bile before and after ipecacuan. 2 cc. bile and 3 cc. water injected into the duodenum at *b*. 60 grains ipecacuan powder in the same fluid injected at *i*.

Experiment 33.		Experiment 34.		Experiment 35.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
0.8		0.35		0.8	
0.85		0.2		0.55	
0.95		0.25		0.25	
0.85		0.3	0.0839 cc.	0.4	
0.8		0.25		*b* ——	
b ——		0.3		0.3	
1.2	0.191 cc.	*e* ——		0.4	0.113 cc.
0.95		0.55		0.5	
0.95		0.4		0.5	
e ——		0.45		*i* ——	
1.4		0.35		0.8	
1.3		0.55		2.0	
1.45		*e′* ——		1.1	0.4 cc.
1.45		0.4		1.4	
1.35	0.272 cc.	0.55		1.5	
1.3		0.55		1.1	
1.2		0.5		1.0	
1.2		*e″* ——		0.9	
e′ ——		0.5		1.2	
1.45		0.7		1.3	
1.3		0.85		1.5	
1.45	0.274 cc.	1.2		1.0	
1.5		0.9		1.0	
1.35		0.9		1.0	
1.2		1.05		0.5	
1.1		1.0		1.0	
1.4		1.05		1.0	
1.25		0.95	0.3167 cc.	1.0	
1.2		1.1		1.05	
		1.05		1.1	
				0.8	
				0.7	

Experiment 36. Dog that had fasted 18 hours. Weight 27.2 kilogrammes. (Fig. 36.)

Fig. 36.



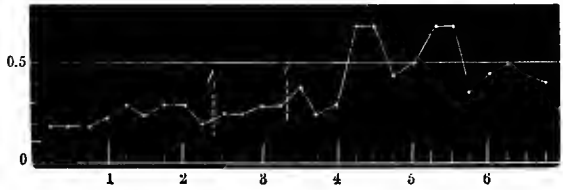
Secretion of bile before and after ipecacuan. 2 cc. bile and 5 cc. water injected into the duodenum at *b*. The same fluid with 60 grains ipecacuan powder injected at *i*.

AUTOPSY.—Stomach normal. The ipecacuan extended along the upper two-thirds of the small intestine, the mucous membrane of which exhibited a slight increase of vascularity, and was covered with thick mucus, but there was no purgation.

Even in much smaller doses, however, ipecacuan excites the liver, as is shown by the two following experiments.

Experiment 37. Dog that had fasted 18 hours. Weight 6.1 kilogrammes. (Fig. 37.)

Fig. 37.

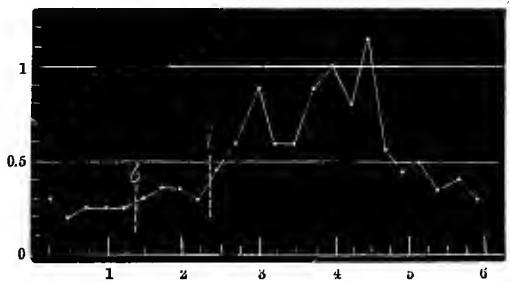


Secretion of bile before and after ipecacuan. 1.5 cc. bile and 2 cc. water injected into the duodenum at *b*. The same fluid with 3 grains of ipecacuan powder injected at *i*.

AUTOPSY.—Thick mucus covering the mucous membrane of upper fourth of small intestine. No purgation.

Experiment 38. Dog that had fasted 17 hours. Weight 6.8 kilogrammes. (Fig. 38.)

Fig. 38.



Secretion of bile before and after ipecacuan. 1.5 cc. bile and 2 cc. water injected into duodenum at *b*. 3 grains ipecacuan powder in the same fluid injected at *i*.

AUTOPSY.—The appearances of the intestine were similar to those observed in the preceding experiment.

Results of Experiments with Ipecacuan.—1. Sixty grains of powdered ipecacuan mixed with a small quantity of bile and placed in the duodenum powerfully stimulated the liver. Even three grains had an effect on a dog weighing 6.8 kilogrammes very nearly as great as the effect of sixty grains on a dog weighing 27.2 kilogrammes; the amount of bile secreted

Experiment 36.		Experiment 37.		Experiment 38.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
1.9		0.2		0.3	
1.7		0.2		0.2	
1.5		0.2		0.25	
1.7		0.25		0.25	
b ——		0.3		0.25	
1.65	0.24 cc.	0.25		*b* ——	
1.55		0.3		0.3	
1.65		0.3		0.35	0.186 cc.
i ——		0.2		0.32	
1.6		*b* ——		0.3	
1.9		0 25		*i* ——	
1.8		0.25	0.18 cc.	0.45	
1.7		0.3		0.6	
1.85		0.3		0.9	
2.4		*i* ——		0.6	
2.6		0.4		0.6	
3.3		0.25		0.9	
3.05		0.3		1.0	0.506 cc.
3.75		0.7		0.8	
2.02		0.7	0.385 cc.	1.15	
3.0		0.45		0.55	
4.25	0.555 cc.	0.5		0.45	
4.0		0.7		0.5	
3.85		0.7		0.35	
3.42		0.35		0.4	
2.6		0.45		0.3	
2.8		0.5			
2.35		0.45			
2.3		0.4			
1.7					

Composition of the Bile before and after Ipecacuan.

TABLE XII.

Experiment 36.	Before.	After.
Water	89.631	89.77
Bile-acids, pigments, cholesterin, fats ...	8.13	8.129
Mucus	1.01	0.87
Ash	1.229	1.231
	100.000	100.000
Velocity of secretion per half-hour	3.2 cc.	6.35 cc.

TABLE XIII.

Experiment 38.	Before.	After.
Water	91.32	91.51
Bile-acids, pigments, cholesterin, fats	6.73	6.73
Mucus	0.98	0.79
Ash	0.97	0.97
	100.00	100.00
Velocity of secretion per half-hour	0.65 cc.	1.9 cc.

These analyses show that, notwithstanding the acceleration of secretion by ipecacuan, the percentage amount of the special biliary constituents remains unchanged.

---

per kilogramme of dog being nearly the same in both cases. 2. The bile secreted under its influence was of normal composition as regards the biliary matter proper. 3. No purgative effect was produced, but there was an increased secretion of mucus in the small intestine. The composition of the bile did not afford any evidence of an increased secretion of mucus having taken place from the glands of the bile-ducts.

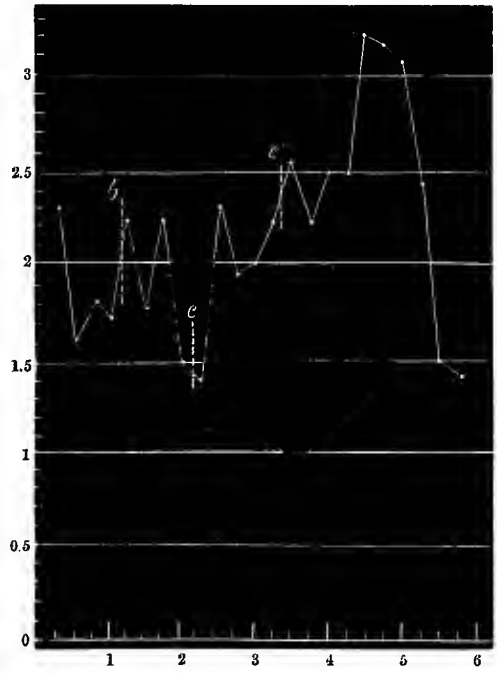
The increased biliary flow that followed ipecacuan could not in these experiments be ascribed to any relaxation of "spasm of the bile-ducts," for that no such thing existed was clearly shown by the free flow of the bile before the substance was given. Nor could it be owing to contraction of the gall-bladder, for the cystic duct was clamped. Nor can it be ascribed to contraction of the bile-ducts, for the increased flow was far too prolonged to be attributable to any such cause. It is therefore certain that this substance, like the others, has the power of stimulating the *secreting* apparatus of the liver. This being now proved as regards the dog, it can scarcely be doubted that the *modus operandi* is the same in man. The results of these experiments will therefore lead to new speculations regarding the pathology of dysentery; for *every step towards greater accuracy of knowledge regarding the* modus operandi *of any therapeutic agent is certainly calculated to advance our knowledge of the true nature of the pathological condition that is relieved or cured by it.*

Action of Colocynth.

Colocynth and jalap are substances whose action on the biliary secretion of the dog has already been investigated by Röhrig (*Stricker's Jahrbücher*, 1873, p. 240). According to that observer croton oil is a powerful cholagogue, and colocynth and jalap stand near it in importance. We have already pointed out the faultiness of Röhrig's method, and have shown (this *Journal*, Vol. x. p. 259) that croton oil is scarcely worthy of being classed amongst cholagogues. It seemed therefore desirable that we should experiment with colocynth and jalap in order to have results comparable with our experiments on other substances.

Experiment 39. Dog that had fasted 16 hours. Weight 26.3 kilogrammes. (Fig. 39.)

Fig. 39.

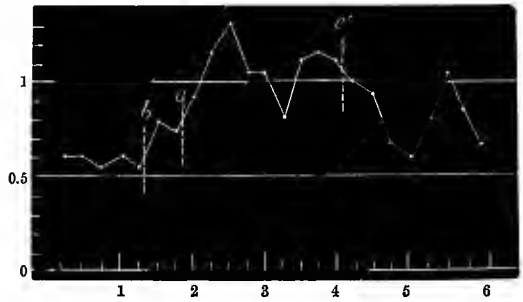


Secretion of bile before and after colocynth. 2 cc. bile and 2 cc. water injected into the duodenum at *b*. The same fluid with 7 grains of powdered colocynth pulp injected at *c*. The same dose repeated at *c'*.

AUTOPSY.—Gastric mucous membrane very vascular. The mucous membrane of the small intestine was intensely vascular throughout its entire length. There was evidence of powerful purgation,—the small intestine containing 82 cc. of fluid.

Experiment 40. Dog that had fasted 16 hours. Weight 16.3 kilogrammes. (Fig. 40.)

Fig. 40.



Secretion of bile before and after colocynth. 3 cc. bile and 3 cc. water injected into the duodenum at *c*. The same repeated at *c'*.

AUTOPSY.—There was increased vascularity throughout the whole length of the mucous membrane of the small intestine, especially marked in the upper part. There was considerable evidence of purgation.

Composition of the Bile before and after Colocynth.

TABLE XIV.

Experiment 39.	Before.	After.
Water	92.99	94.13
Bile-acids, pigments, cholesterin, fats ...	5.49	4.70
Mucus	0.90	0.70
Ash	0.62	0.47
	100.00	100.00
Velocity of secretion per half-hour	3.4 cc.	6.35 cc.

TABLE XV.

Experiment 40.	Before.	After.
Water	91.48	91.72
Bile-acids, pigments, cholesterin, fats ...	6.85	6.69
Mucus	0.83	0.77
Ash	0.84	0.82
	100.00	100.00
Velocity of secretion per half-hour	1.15 cc.	2.35 cc.

These analyses show that colocynth renders the bile more watery, although it at the same time increases the secretion of the special biliary matters.

In Exp. 40, the pulse became very weak towards the close of the experiment, and it may be that this weakness rendered the effect of the colocynth upon the liver less than it otherwise might have been. Be this as it may, we did not think it necessary to perform another experiment, for the first experiment with this substance may be regarded as sufficient.

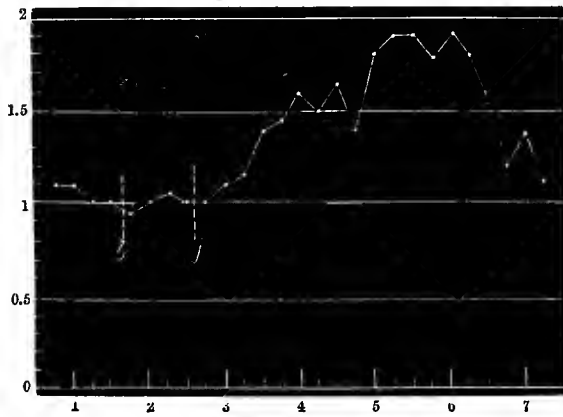
Results of the Experiments with Colocynth.—1. Colocynth is a hepatic stimulant of considerable power. It renders the bile more watery but nevertheless increases the secretion of biliary matter. 2. It is also a powerful stimulant of the intestinal glands.

ACTION OF JALAP.

Experiment 41. Dog that had fasted 17 hours. Weight 25 kilogrammes. (Fig. 41.)

AUTOPSY.—The jalap had extended along about four-fifths of the small intestine, the mucous membrane of which was more vascular than usual, especially so at the lower part of the duodenum. The purgative effect was considerable—there being 64 cc. of fluid in the intestine. The fluid was of a very watery character.

Fig. 41.



Secretion of bile before and after jalap. 2.5 cc. bile and 2.5 cc. water injected into the duodenum at *b*. 30 grains of jalap powder in the same fluid injected at *j*.

Experiment 39.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	
2.3	
1.6	
1.8	
b ——	
1.7	
2.2	
1.75	0.2908 cc.
2.2	
1.5	
c ——	
1.4	
2.3	
1.95	
2.0	
2.2	
c′ ——	
2.55	
2.2	
2.5	
2.5	
3.2	
3.15	0.452 cc.
3.05	
2.45	
1.5	
1.4	

Experiment 40.

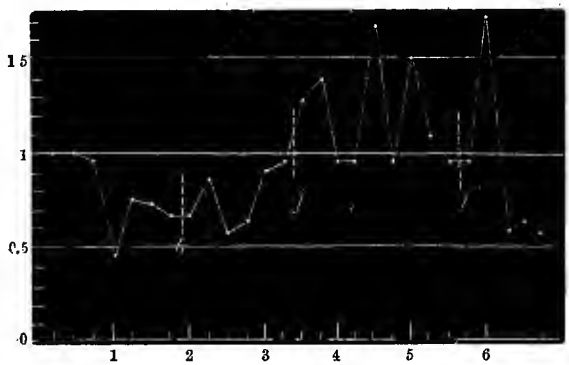
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	
0.6	
0.6	
0.55	
0.6	
0.55	
b ——	0.165 cc.
0.8	
0.75	
c ——	
0.9	
1.15	
1.3	0.279 cc.
1.05	
1.05	
0.8	
1.1	
1.15	
1.1	
c′ ——	
1.0	
0.95	
0.65	
0.6	
0.8	
1.05	
0.85	
0.65	

Experiment 41.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.	
1.1	
1.1	
1.0	
1.0	
b ——	
0.95	
1.0	0.16 cc.
1.05	
1.0	
j ——	
1.0	
1.1	
1.15	
1.4	
1.45	
1.6	
1.5	
1.65	
1.4	
1.8	
1.9	
1.9	
1.8	0.296 cc.
1.9	
1.8	
1.6	
1.2	
1.4	
1.1	

Experiment 42. Dog that had fasted 20 hours. Weight 11.8 kilogrammes. (Fig. 42.)

Fig. 42.



Secretion of bile before and after jalap. 3 cc. water and 2 cc. bile injected into the duodenum. 20 grains jalap powder in the same fluid injected at *j*, and again at *j'*.

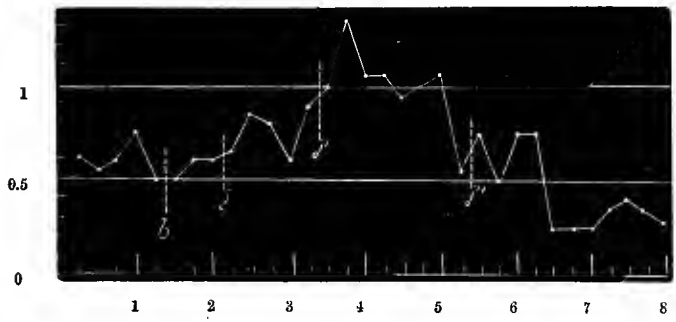
AUTOPSY.—Profuse purgative action throughout the whole extent of intestine. Vascularity of mucous membrane of small intestine somewhat increased, most marked in the duodenum.

The rapid fall in the bile-secretion towards the close of this experiment probably resulted from the purgation. It is to be noted that in *Exp.* 42, a *larger* dose of jalap was given (40 grains) to a dog less than half the size of the subject of *Exp.* 41. This is doubtless the cause of the greater effect on the liver and on the intestinal glands in *Exp.* 42. The effect of a still larger dose in a dog of nearly the same weight as No. 42 is instructive. (See Fig. 43.)

Experiment 43. Dog that had fasted 22 hours. Weight 12.3 kilogrammes. (Fig. 43.)

AUTOPSY. 20 cc. of fluid had been injected into the duodenum, much of which had probably been absorbed; the small intestine, however, contained in its upper third 117 cc. of watery fluid, showing that a profuse purgative action was taking place. The jalap had extended along only a third of the small intestine.

Fig. 43.



Secretion of bile before and after jalap. 2 cc. bile and 3 cc. water injected into duodenum at *b*. 20 grains jalap powder in the same fluid injected at *j*, *j'*, and *j''*.

The fall of the bile-secretion towards the close of the experiment is only another illustration of the fact often witnessed by us—*that severe purgation diminishes the secretion of bile.*

Composition of the Bile before and after Jalap.

TABLE XVI.

Experiment 41.	Before.	After.
Water	89.31	89.75
Bile-acids, pigments, cholesterin, fats ...	8.41	8.05
Mucus	0.93	0.87
Ash	1.35	1.33
	100.00	100.00
Velocity of secretion per half-hour	2.1 cc.	3.7 cc.

TABLE XVII.

Experiment 42.	Before.	After.
Water	87.91	88.19
Bile-acids, pigments, cholesterin, fats ...	9.94	9.87
Mucus	0.73	0.52
Ash	1.42	1.42
	100.00	100.00
Velocity of secretion per half-hour	1.4 cc.	2.55 cc.

Experiment 42.		Experiment 43.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.0		0.6	
1.0		0.55	
0.95		0.6	
0.45		0.75	
0.75		0.5	
0.7		*b* —	
0.65		0.5	0.178 cc.
b —		0.6	
0.65		0.6	
0.85		*j* —	
0.55		0.65	
0.6	0.254 cc.	0.85	
0.9		0.8	
0.95		0.6	
j —		0.9	
1.25		*j′* —	
1.35		1.0	
0.95		1.35	
0.95		1.05	0.357 cc.
1.65		1.05	
0.95	0.436 cc.	0.95	
1.5		1.0	
1.05		1.05	
0.95		0.55	
j′ —		*j″* —	
0.95		0.75	
1.75		0.5	
0.55		0.75	
0.6		0.75	
0.55		0.25	
		0.25	
		0.25	
		0.35	
		0.4	0.113 cc.
		0.35	
		0.3	

Results of Experiments with Jalap.—1. Jalap is a hepatic stimulant of considerable power. It renders the bile more watery, but at the same time increases the secretion of biliary matter. 2. Its effect on the liver is however far less notable than its effects on the intestinal glands. Its hydrogogue cathartic effects on these were fully manifested in these experiments.

EXPERIMENTS ON THE BILIARY SECRETION OF THE DOG. By Prof. RUTHERFORD and M. VIGNAL.

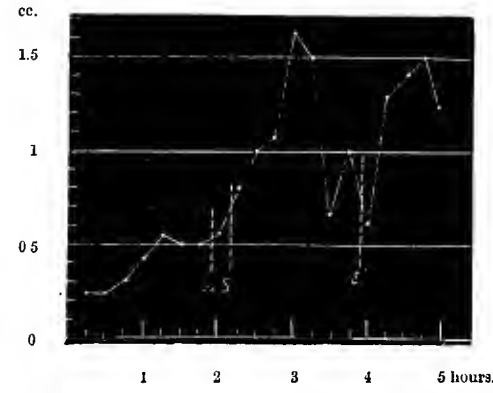
THIRD SERIES.

ACTION OF SODIUM SULPHATE.

WORKS on Therapeutics generally make no mention of any cholagogue action of this substance. In the fourth edition of Garrod's *Materia Medica*, however, it is stated, that in addition to its action as a saline purgative it "probably influences the biliary secretion."

Experiment 44. Dog that had fasted 19 hours. Weight 19.5 kilogrammes. (Fig. 44.)

Fig. 44.

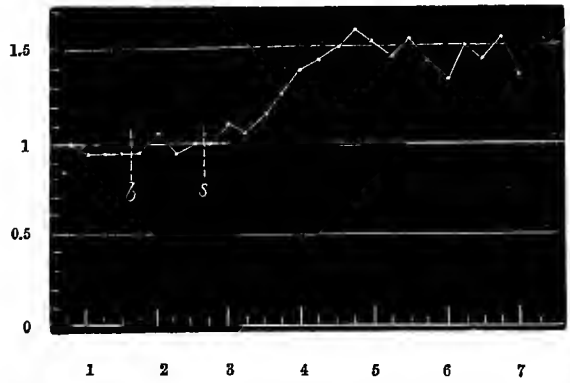


Secretion of bile before and after sodium sulphate. 21 cc. water injected into duodenum at *w*. 60 grains sodium sulphate in 12 cc. water injected at *s*, and again at *s'*.

AUTOPSY. Evidence of decided purgative action in small intestine, the mucous membrane of which exhibited a considerably increased vascularity.

Experiment 45. Dog that had fasted 20 hours. Weight 15.7 kilogrammes. (Fig. 45.)

Fig. 45.



Secretion of bile before and after sodium sulphate. 3 cc. bile and 5 cc. water—heated to 37°C.—injected into duodenum at *b*. 508 grains sodium sulphate—in the same fluid heated to 37°C., injected at *s*.

AUTOPSY. Mucous membrane of whole length of small intestine slightly reddened. The small intestine contained 147 cc. of clear fluid with greenish flakes; thus affording evidence of a decided purgative effect.

Results of Experiments with Sodium Sulphate.—Doses of 60 grains twice repeated (Experiment 44), and a single dose of 508 grains (Experiment 45), increased the biliary secretion Sodium sulphate is undoubtedly, therefore, a hepatic stimulant, but not of great power, for even in the second case the hourly secretion of bile per kilogramme of body-weight did not rise higher than 0.388 cc. per hour. The positive character of this result is important, because it is well known that the waters of Carlsbad have a cholagogue action, and although they contain in addition to sodium sulphate, sodium carbonate, sodium chloride, potassium sulphate, and small quantities of other substances, sodium sulphate is the principal salt, and to it the cholagogue action is doubtless chiefly due.

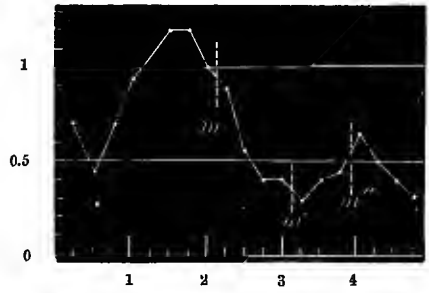
Sodium sulphate, however, has for a considerable time been—in practical medicine—almost entirely superseded by magnesium sulphate, on account of its "more agreeable taste"

(Garrod): we therefore performed the two following experiments to determine whether or not this substance is a cholagogue.

Action of Magnesium Sulphate.

Experiment 46. Dog that had fasted 17 hours. Weight 5.4 kilogrammes. (Fig. 46.)

Fig. 46.

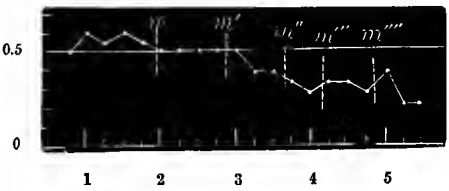


Secretion of bile before and after magnesium sulphate. 60 grains in 6 cc. water injected into duodenum at *m*, *m'* and *m''* (180 grains given in all).

Autopsy. Great purgative action in upper half of small intestine. Mucous membrane intensely reddened.

Experiment 47. Dog that had fasted 17 hours. Weight 8.2 kilogrammes. (Fig. 47.)

Fig. 47.



Secretion of bile before and after magnesium sulphate. 60 grains in 12 cc. water at *m*. 60 grains in 6 cc. water at *m'*, *m''*, *m'''*, and 120 grains in 12 cc. water at *m''''*, all injected into duodenum (360 grains given in all).

Autopsy. Small intestine contained 90 cc. of fluid, whereas only 42 cc. had been injected. There was, therefore, evidence of decided purgation, and there was intense irritation of the mucous membrane in the upper half of the small intestine.

Results of Experiments with Magnesium Sulphate.—Experiment 46—but especially experiment 47—clearly show that, unlike sulphate of soda, magnesium sulphate has no cholagogue action. The curve in experiment 47 exhibits remarkably well the effect on the secretion of bile, produced by a substance that stimulates the intestinal glands, but not the liver. *In such a case the biliary secretion is simply diminished.*

Experiment 44.		Experiment 45.		Experiment 46.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
0.25		1.00		0.70	
0.25		0.95		0.45	
0.30		0.95		0.70	0.564 cc.
0.40		0.95		0.95	
0.55		*b* ——		0.95	
0.50		0.95		1.20	
0.50	0.107 cc.	1.05	0.251 cc.	1.20	
w ——		0.95		1.00	
0.55		1.00		*m* ——	
s ——		*s* ——		0.90	
0.80		1.00		0.55	
1.00		1.10		0.40	
1.05		1.05		0.40	
1.65	0.266 cc.	1.15		*m′* ——	
1.50		1.25		0.30	
0.65		1.40		0.40	
1.00		1.45		0.45	
s′ ——		1.50		*m″* ——	
0.60		1.60	0.388 cc.	0.65	
1.30		1.55		0.50	0.342 cc.
1.40		1.45		0.40	
1.50	0.279 cc.	1.55		0.30	
1.25		1.45			
		1.35			
		1.50			
		1.45			
		1.55			
		1.35			

Action of Potassium Sulphate.

Potassium sulphate is sometimes employed as a purgative agent, but no mention is made in the books, of its having any action on the liver. Dr Wade of Birmingham, however, informed us that he finds this substance a cholagogue in man,

and at his request we tested by our method its action on the liver of the dog.

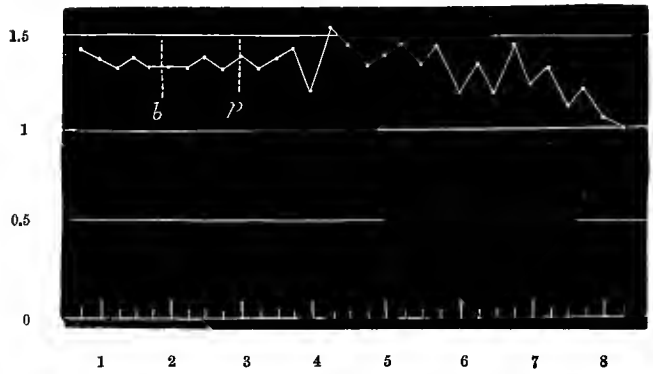
Experiment 47.		Experiment 48.		Experiment 49.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
0.50		1.45		1.80	
0.60		1.40		1.90	
0.55	0.28 cc.	1.35		1.70	
0.60		1.40		1.65	0.316 cc.
0.55		1.32		1.65	
m ——		*b* ——		1.70	
0.50		1.32		*p* ——	
0.50		1.32	0.315 cc.	1.80	
0.50		1.40		1.70	
0.50		1.32		1.90	
m′ ——		*p* ——		1.80	
0.50		1.40		1.90	
0.40		1.32		2.05	
0.40		1.40		2.07	
m″ ——		1.42		2.10	
0.35		1.20		2.25	
0.30		1.52		2.37	
m‴ ——		1.42		2.45	
0.35		1.35		2.40	
0.35		1.40		2.45	
0.30		1.42		2.50	
m⁗ ——		1.35		2.47	
0.40	0.146 cc.	1.42		2.55	
0.25		1.20		2.55	0.47 cc.
0.25		1.35		2.57	
		1.20		2.45	
		1.45		2.40	
		1.27		2.30	
		1.37		2.40	
		1.17		2.40	
		1.22	0.266 cc.	2.20	0.352 cc.
		1.10		1.95	
		1.02		1.20	

Experiment 48. Dog that had fasted 17 hours. Weight 17 kilogrammes. (Fig. 48.)

AUTOPSY. Small intestine contained 137 cc. greenish fluid with mucous flakes. The mucous membrane exhibited increased vascularity with small ecchymoses in its upper fourth.

In this case, therefore, this substance irritated the intestine and produced purgation, but did not excite the liver. It was decided to give in the next case a larger dose.

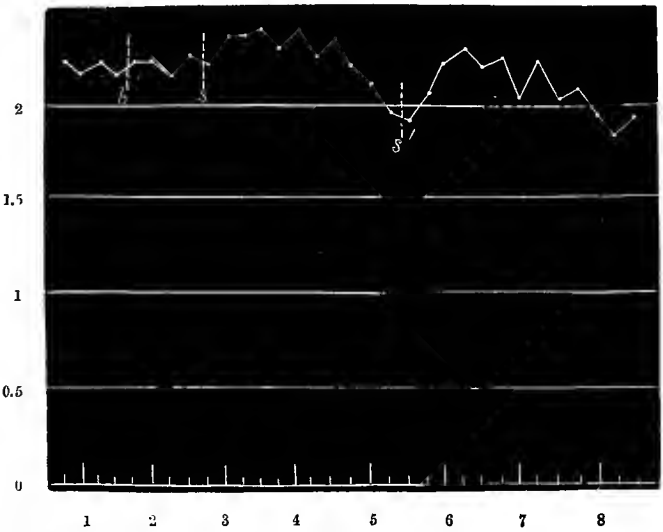
Fig. 48.



Secretion of bile before and after potassium sulphate. 2½ cc. bile and 16 cc. water injected into duodenum at *b*. The same with 124 grains potassium sulphate heated to 37°C. injected at *p*.

Experiment 49. Large dog that had fasted 17 hours. Its weight unfortunately was not recorded. (Fig. 49.)

Fig. 49.



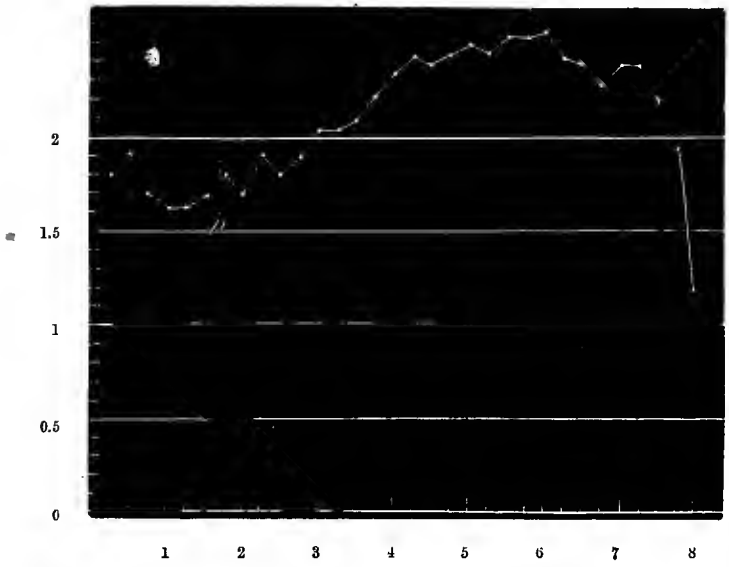
Secretion of bile before and after potassium sulphate. 2½ cc. bile and 35 cc. water injected into duodenum at *b*, the same with 142 grains potass. sulph. injected at *s* and again at *s'*.

AUTOPSY. Small intestine contained 143 cc. watery fluid. The vascularity of the mucous membrane in the whole length of the small intestine was slightly increased.

There being in this case evidence of a slight increase of the biliary secretion, another experiment was thought desirable.

Experiment 50. Dog that had fasted 17 hours. Weight 21.5 kilogrammes. (Fig. 50.)

Fig. 50.



Secretion of bile before and after 232 grains potassium sulphate dissolved in 32 cc. water at 37°C. and injected into duodenum at *p*.

AUTOPSY. Increased vascularity of mucous membrane in whole length of small intestine. The small intestine contained 90 cc. clear brownish fluid with numerous mucous flakes. There was, therefore, evidence of considerable purgative action.

Results of Experiments with Potassium Sulphate.—Experiment 50 clearly shows that potassium sulphate is undoubtedly a hepatic stimulant. The dose of 232 grains, given in this case to a full-sized dog, was just the maximum dose for a man. The negative effect of 124 grains in experiment 48, and the slight effect of 142 grains twice repeated in experiment 49,

suggest that this substance is uncertain in its action on the liver. Regarding its action on the intestinal glands, however, there was no uncertainty, for its purgative effect was pronounced in all the three experiments. Possibly the sparing solubility of the salt may render its absorption into the portal vein uncertain. The bile given along with the salt in experiments 5 and 6 had probably nothing whatever to do with the result. The result of experiment 50 completely supports Dr Wade's opinion, that potassium sulphate is a cholagogue. Indeed, the amount of bile secreted per kilogramme of body-weight under its influence in experiment 50 was greater than in either of the experiments with sodium sulphate (44 and 45). The apparent uncertainty, however, in the action of potassium sulphate must not be lost sight of.

Action of Sodium Phosphate.

Sodium phosphate is described in the text-books as a mild saline purgative; nothing being said about its action as a cholagogue. Professor Stephenson of Aberdeen, however, has found it specially useful for children when there is a deficiency of bile in the discharges (*Edinburgh Medical Journal*, 1867, Vol. XIII. p. 336). The dose as a purgative for a man is 120—480 grains.

Experiment 51. Dog that had fasted 20 hours. Weight 26.9 kilogrammes. (Fig. 51.)

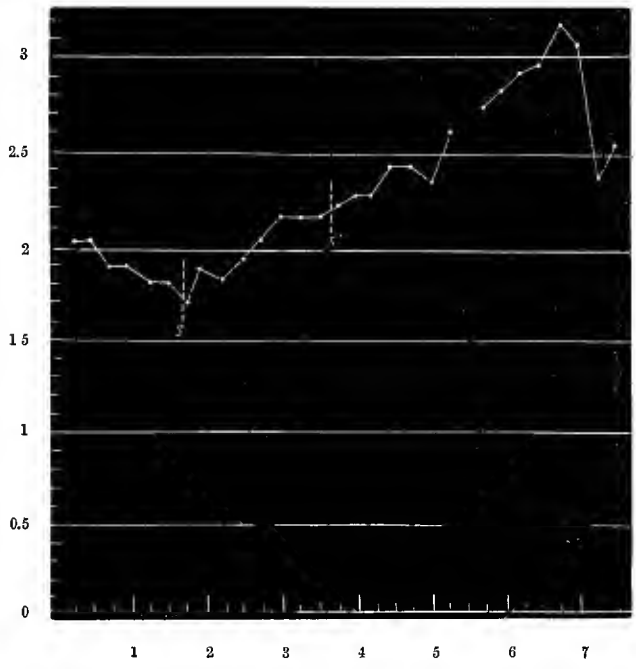
Autopsy. Somewhat increased vascularity of mucous membrane of small intestine. Evidence of a very decided purgative effect: the contents of the small intestine being of a very watery character.

Table XVIII.

Composition of the Bile before and after Sodium Phosphate.

Experiment 51.	Before.	After.
Water	84.69	85.15
Bile-acids, pigments, cholesterin, fats	13.23	12.91
Mucus	1.01	0.93
Ash	1.07	1.01
	100.00	100.00
Velocity of secretion per half-hour	3.6 cc.	5.5 cc.

Fig. 51.



Secretion of bile before and after sodium phosphate. 77 grains in 15 cc. water injected into duodenum at *s*, and 124 grains in 25 cc. water injected at *s'*.

Results of Experiments with Sodium Phosphate.—1. This substance is undoubtedly a hepatic stimulant of very considerable power. 2. Although it renders the bile more watery, it increases the amount of biliary matter secreted per unit of time. 3. While acting as a purgative, it irritates the intestinal mucous membrane very slightly.

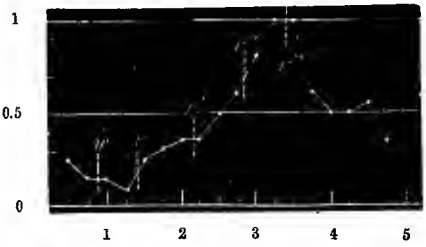
The results of experiment 51 were so satisfactory—both doses of the substance producing an effect—that it was thought needless to repeat it, as it confirms Dr Stephenson's observations on the human subject, adding to these, however, the definite knowledge that it has the power of actually increasing the flow of the bile, and that it does so by stimulating the hepatic cells.

Action of Rochelle Salt.

Nothing is stated in the books regarding any cholagogue action of this substance. Its dose as a purgative for a man is from 120 to 240 grains.

Experiment 52. Dog that had fasted 17 hours. Weight 5.2 kilogrammes. (Fig. 52.)

Fig. 52.



Secretion of bile before and after tartrate of potash and soda. 10 cc. water injected into duodenum at *w*. The same with 60 grains Rochelle salt injected at *r*, *r'*, *r''*, and *r'''* (240 grains given in all).

No autopsy.

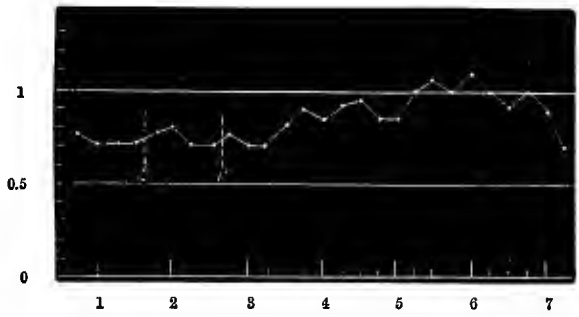
Considering the small size of this animal, the exciting effect of the salt on the liver was very remarkable, the secretion of bile per kilogramme of body-weight per hour being raised to 0.653 cc. The fall in the secretion towards the close of the experiment was doubtless owing to purgative action taking place.

Experiment 53. Dog that had fasted 20 hours. Weight 12.5 kilogrammes. (Fig. 53.)

Autopsy. Small intestine contained 130 cc. of a clear mucous fluid. Mucous membrane of small intestine exhibited a slightly increased vascularity.

Results of Experiments with Rochelle Salt.—It is certainly a hepatic stimulant. Experiment 52 shows what a rapid secretion of bile it called forth in a liver that was nearly passive before it was given. The effect was by no means so remarkable in

Fig. 53.



Secretion of bile before and after Rochelle salt. 3 cc. bile and 55 cc. water heated to 37°C. injected into duodenum at *b*. The same with 463 grains Rochelle salt heated to 37°C. injected at *r*.

experiment 53, where the liver was relatively more active before the substance was given. Probably the latter affords a better general indication than the former, of the power of this substance as a cholagogue, and it must be remembered that in both cases, considering the size of the animals as compared with man, the doses were large; so that, on the whole, it may be anticipated that observations on man—now that we specially direct attention to the matter—will show that this substance is a cholagogue, but not a powerful one.

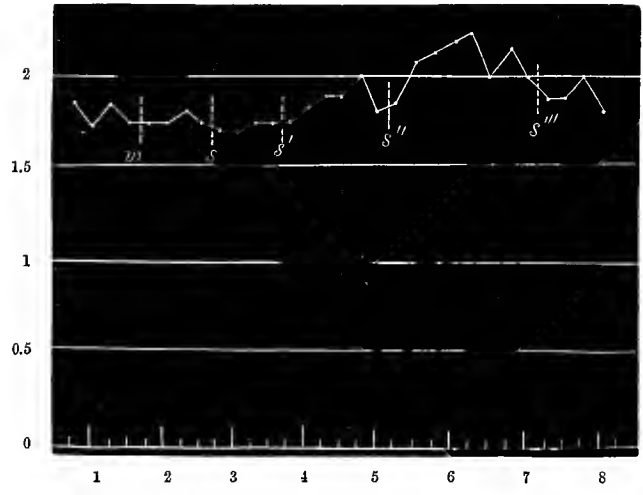
Action of Sodium Chloride.

Sodium chloride is a cathartic when given in doses of 120 to 240 grains. It is not known to be a cholagogue, but as it is contained in considerable quantity in the mineral waters of Carlsbad, Ems, Friedrichshalle, that have a reputation in abnormal conditions of the liver, we thought it desirable to test its action on this organ.

Experiment 54. Dog that had fasted 18 hours. Weight 25 kilogrammes. (Fig. 54.)

Autopsy. The small intestine contained 203 cc. of fluid, with numerous mucous flakes. As only 50 cc. of fluid had been

Fig. 54.



Secretion of bile before and after sodium chloride. 10 cc. water injected into duodenum at *w*. The same with 120 grains sodium chloride injected at *s*, *s'*, *s''*, *s'''* (480 grains given in all).

injected, decided purgative action had taken place. The vascularity of the mucous membrane was slightly increased.

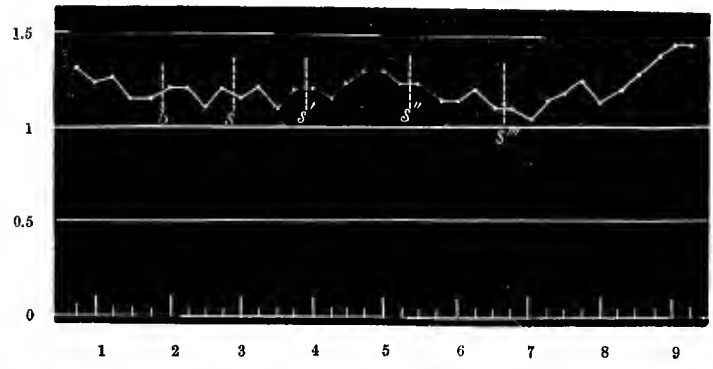
Result of Experiment with Sodium Chloride.—Inasmuch as the first three doses of sodium chloride, amounting in the aggregate to 360 grains, produced scarcely any effect on the secretion of bile, it may be concluded that this substance is a very feeble hepatic stimulant. Another experiment did not appear to be required.

Action of Sodium Bicarbonate.

Experiment 55. Dog that had fasted 18 hours. Weight 16.3 kilogrammes. (Fig. 55.)

Autopsy. The vascularity of the mucous membrane of the small intestine was slightly increased. The viscus contained 60 cc. of a greenish mucous fluid.

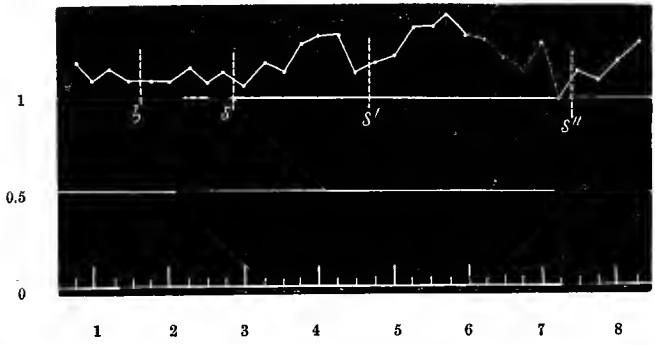
Fig. 55.



Secretion of bile before and after sodium bicarbonate. 5 cc. water and 2 cc. bile injected into duodenum at *b*. The same with 31 grains sodium bicarbonate injected at *s*, *s'* and *s''*. 15 cc. water with 2 cc. bile and 124 grains sodium bicarbonate injected at *s'''* (217 grains given in all).

Experiment 56. Dog that had fasted 18 hours. Weight 19.9 kilogrammes. (Fig. 56.)

Fig. 56.



Secretion of bile before and after sodium bicarbonate. 5 cc. water and 2.5 cc. bile injected into duodenum at *b*. The same with 64 grains sodium bicarbonate injected at *s*, *s'*, and *s''* (192 grains given in all).

Result of Experiments with Sodium Bicarbonate.—In experiment 55, the amount of bile secreted per kilogramme of body-weight during the first hour was 0.294 cc., during the seventh hour it was 0.287 cc.; and during the last hour—after 217

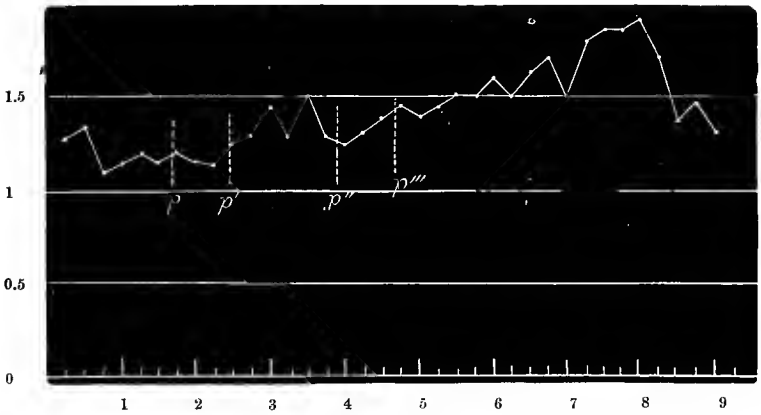
grains sodium bicarbonate had been given, it was 0.341 cc. In experiment 56 the secretion during the first hour was 0.23 cc. per kilogramme of body-weight; during the fifth hour, when the secretion was at its height, it was 0.28 cc. per kilogramme, 128 grains of sodium bicarbonate having been given. It is, therefore, evident, that this substance has scarcely any effect on the secretion of bile. Nevertheless, the slight effect perceptible in experiment 56 more especially, indicates an exciting influence on the liver, although an extremely feeble one.

Experiment 51.		Experiment 52.		Experiment 53.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.		cc.	
2.05		0.25		0.75	
2.07		0.15		0.70	
1.90		*w* ——	0.115 cc.	0.70	
1.90	0.278 cc.	0.15		0.70	
1.80		0.05		*b* ——	
1.80		*r* ——		0.75	
s ——		0.25		0.80	0.236 cc.
1.70		0.30		0.70	
1.90		0.35		0.70	
1.80		*r′* ——		*r* ——	
1.95		0.35		0.75	
2.07		0.50		0.70	
2.15		0.60		0.70	
2.17		*r″* ——		0.80	
2.17		0.80		0.90	
s′ ——		1.00		0.85	
2.20		*r‴* ——	0.653 cc.	0.90	
2.27		1.00		0.95	
2.25		0.60		0.85	
2.40		0.50		0.85	
2.40		0.50		1.00	
2.30		0.55		1.05	0.332 cc.
2.60		0.35		1.00	
lost.				1.10	
2.70				1.00	
2.80				0.90	
2.90				1.00	
2.95	0.448 cc.			0.90	
3.15				0.70	
3.05					
2.30					
2.57					

Action of Potassium Bicarbonate.

Experiment 57. Dog that had fasted 18 hours. Weight 19.3 kilogrammes. (Fig. 57).

Fig. 57.



Secretion of bile before and after potassium bicarbonate. 31 grains in 8 cc. water injected into duodenum at *p*, *p'*, and *p''*. 108 grains in 8 cc. water injected at *p'''*. (201 grains given in all.)

Autopsy.—53 cc. of a clear brownish fluid, with numerous mucous flakes in small intestine. Vascularity of mucous membrane considerably increased.

Result of Experiment with Potassium Bicarbonate.—201 grains of this substance increased the secretion of bile but not to a great extent, for the bile-secretion per hour did not rise higher than 0.384 cc. per kilogramme of body-weight. Seeing that 31 grains produced no effect, it may be safely inferred that the dose of 10 or 15 grains often taken by a man does not appreciably affect his biliary secretion.

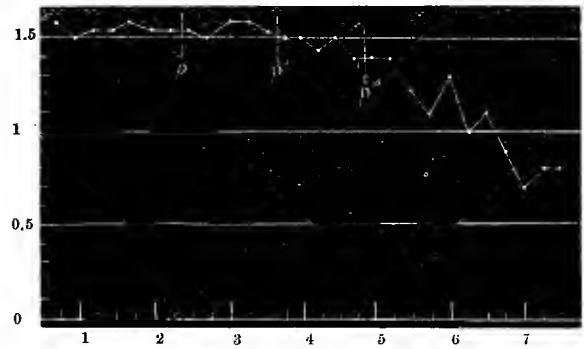
Action of Iodide of Potassium.

Potassium iodide is sometimes administered in hepatic affections, in the hope that it may produce an "alterative"

effect. On that account it seemed desirable to ascertain whether or not it affects the biliary secretion.

Experiment 58. Dog that had fasted 18 hours. Weight 17 kilogrammes (Fig. 58).—10 grains of potassium iodide in 3 cc. of water were injected into the duodenum at p, 20 grains at p', and 30 grains at p''. There was no increase of secretion, but,

Fig. 58.



Secretion of bile before and after potassium iodide. At p 10 grains, at p' 20 grains, and at p'' 30 grains in 3 cc. of water injected into the duodenum.

on the contrary, a rather greater fall than is usually observed in a normal case. A repetition of the experiment was therefore necessary.

Necropsy.—54 cc. of a thick yellowish mucous fluid found in the small intestine, thus affording evidence of a slight purgative action.

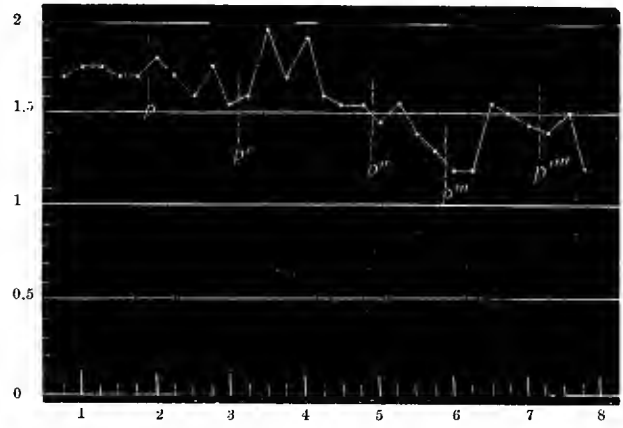
Experiment 58A. Dog that had fasted 19 hours. Weight 16.9 kilogrammes (Fig. 58A).—5 grains of potassium iodide in 2 cc. of water were injected into the duodenum at p, 10 grains in 2 cc. of water at p', 20 grains in 5 cc. of water at p'', 30 grains in 5 cc. of water at p''', and 40 grains in 8 cc. of water at p''''. The trifling increase of secretion after the second and fourth doses may be discarded, and the fall of secretion as the experiment advanced might very probably have been equally marked had nothing been given.

Necropsy.—Small intestine contained 25 cc. of a clear mucous fluid, indicating a slight purgation; for, though 22 cc.

of water had been injected, much of it had doubtless been absorbed.

Result of Experiments with Potassium Iodide.—This substance does not appear to affect the biliary secretion.

Fig. 58A.



Secretion of bile before and after potassium iodide. At p 5 grains in 2 cc. of water, at p' 10 grains in 2 cc. of water, at p'' 20 grains in 5 cc. of water, at p''' 30 grains in 5 cc. of water, and at p'''' 40 grains in 8 cc. of water, injected into the duodenum.

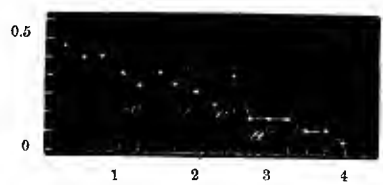
Action of Ammonium Chloride.

According to Garrod (*Op.* viii. p. 51), chloride of ammonium is "by some considered a cholagogue." The most valuable evidence which we have regarding the action of this substance is that furnished by Dr Stewart of Brecon (*Op.* ix.). The large experience in the treatment of hepatic affections acquired by Dr Stewart in India has led him to regard ammonium chloride as an invaluable agent in the treatment of active hepatic congestion, chronic hepatitis, and in "torpor of the liver," associated with congestion of the organ and lithæmia. Many such cases he has seen cured by from ten to twenty grain doses, given twice or thrice daily, with attention to diet, rest, and such other general indications. The drug produces diuresis, a sensation of warmth beginning in the epigastrium and

gradually extending over the whole body, diaphoresis, exhilaration of the nervous system, and an undoubted effect on the liver, as shown, not only by gradual disappearance of the symptoms referable to hepatic congestion, but by other and more immediate signs, "peculiarly and directly referable to the liver and related parts." Thus, within from five minutes to half an hour after a dose of the salt, the patient may experience one or more "shocks" as of "something giving way," or a "pricking" or "gnawing" sensation in the hepatic region. In addition to these symptoms a full dose increases intestinal peristalsis, "as evidenced by the twisting and other movements experienced in the situation of the duodenum, or all over the abdomen, and which, at times, are more sensibly felt in the situation of the umbilicus, or in the inguinal region. The abdominal muscles may also be thrown into tonic contractions, which are perceptible at times to both sight and touch." "Torpor of the liver," and functional derangements attended by lithæmia (Murchison), associated with congestion of the liver, want of sleep, and depression of spirits, are benefited in a remarkable manner by a course of ammonium chloride, with careful attention to diet and regimen. In such cases, he has known a few twenty-grain doses of the salt "remove symptoms of disordered liver, restore sleep, and revive the drooping spirits, after the failure of other remedies." Dr Stewart, however, nowhere says that he ever observed any cholagogue effect of this remedy.

Experiment 59. Dog that had fasted 18 hours. Weight 7 kilogrammes (Fig. 59).

Fig. 59.



Secretion of bile before and after ammonium chloride. 6 cc. water injected into duodenum at *w*. The same with 6 grains ammonium chloride, injected at *a*, and again at *a'* and *a''* (18 grains given in all).

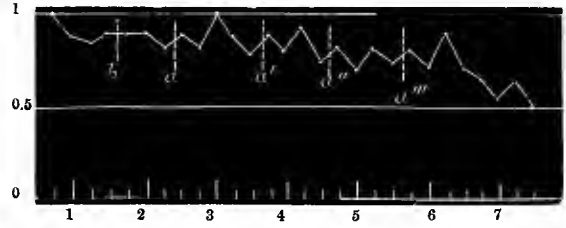
NECROPSY.—Small intestine, in nearly its whole length

contained a large quantity of a very watery fluid. The vascularity of the mucous membrane was only slightly increased.

Experiment 59A. Dog that had fasted 20 hours. Weight 13.7 kilogrammes (Fig. 59A).

NECROPSY.—Somewhat increased vascularity of the mucous

Fig. 59A.



Secretion of bile before and after ammonium chloride. ½ cc. bile and 5 cc. water injected into duodenum at *b*. The same with 10 grains ammonium chloride injected at *a*. At *a'* the same with 20 grains, at *a''* the same with 40 grains, at *a'''* the same with 60 grains.

membrane of the upper three-fourths of the small intestine. There was evidence of a moderate purgative effect.

Result of Experiments with Ammonium Chloride.—The two experiments with this substance show that doses capable of stimulating the intestinal glands did not excite the liver. The effect on the biliary secretion is comparable to that of sulphate of magnesia (p. 69), or other substances having a stimulant effect on Lieberkühn's glands, but not on the liver. In proportion to the body-weight, the doses we gave to the dog were greater than those given to man, and therefore it need not be expected that, in the doses recommended by Dr. Stewart, a purgative effect should be observed in man. Inasmuch, therefore, as these experiments give no evidence of any stimulant action of this substance on the liver, and seeing that in the human subject also there is no certain evidence of its having any *direct* cholagogue action, one is led to ask whether the effects observed by Dr Stewart, in cases of chronic hepatic torpidity, may not have been the result of some indirect action on the liver, due to a slight but prolonged increase of the intestinal secretion, or to some effect on the system generally.

Our experiments supplement Dr Stewart's observations, and plainly narrow the range of speculation in searching for a rational theory of the action of the drug in hepatic congestion.

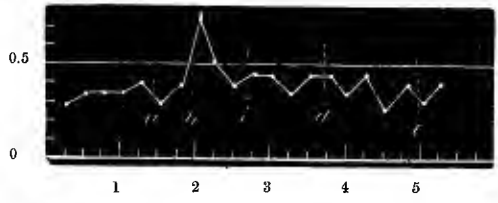
Action of Nitro-hydrochloric Acid.

The dilute nitro-hydrochloric acid employed by us was prepared by mixing 3 cc. nitric acid with 4 cc. hydrochloric acid, and, after an interval of twenty-four hours, adding 25 cc. water (*British Pharmacopœia*). The dose for a man is from 5 to 20 minims.

The employment of this substance in hepatic disorder was first recommended by Dr Scott of Bombay, who used it largely in congestion of the liver. It was administered as a foot-bath, and also internally. Its effects, however, were by some held to be so doubtful, that its use appears to have been abandoned for a time (Christison, *Op.* xii. p. 41). Annesley, Martin, and others —experienced in the diseases of India—have, however, supported the opinion held by Scott. Wood (*Op.* xi, p. 88) maintains, from his own observation, that it increases the flow of the bile.

Experiment 60. A small dog (weight not ascertained) that had fasted 17 hours (Fig. 60).—20 cc. water injected into

Fig. 60.



Secretion of bile before and after nitro-hydrochloric acid. 20 cc. water injected into duodenum at *a*. The same with 20 minims dilute nitro-hydrochloric acid injected at *b*, *c*, *d*, and *e*.

duodenum at *a*. The same with 20 minims dilute nitro-hydrochloric acid injected at *b*, *c*, *d*, and *e*.

Necropsy.—The duodenal mucous membrane was slightly congested. There was no evidence of purgation.

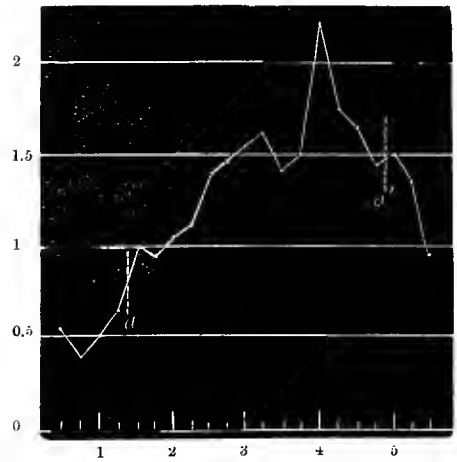
Experiment 60A. Dog that had fasted 17 hours. Weight 17.7 kilogrammes (Fig. 60A).—40 minims dilute nitro-hydrochloric acid in 8 cc. water injected into duodenum at *a*, and again at *a'*.

NECROPSY.—There was slight congestion of the upper part of the small intestine to the extent of about 10 inches. In the

Experiment 60A.

Secretion of bile per 15″	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.55		1.60	
0.40		1.40	
0.50	0.117 cc.	1.50	
0.65		2.20	0.392 cc.
a ——		1.72	
1.00		1.62	
0.95		1.45	
1.05		a'——	
1.10		1.50	
1.40		1.35	
1.45		0.95	
1.55			

Fig. 60A.



Secretion of bile before and after nitro-hydrochloric acid. 40 minims dilute nitro-hydrochloric acid in 8 cc. of water injected into duodenum at a, and again at a'.

duodenum the mucous membrane had a yellowish-grey appearance, as if it had been slightly corroded by an acid. There was no evidence of any purgative effect.

Results of Experiments with Nitro-hydrochloric Acid.—The positive effect of the acid in Experiment 60A is in remarkable contrast to the negative result observed in Experiment 60. In consequence of the positive result in the former case, and seeing that it completely agrees with observations on man, we did not think it necessary to perform another experiment. In view of the positive effect in 60A, we do not attach any importance to the negative result of Experiment 60; for the animal was a small one, and in such cases we have found that undoubted cholagogues sometimes fail to act, probably because of the effect of the shock of the operation on the liver. Strong dogs of considerable size should always be selected for such experiments. Experiment 60A shows that dilute nitro-hydrochloric acid is a hepatic stimulant of considerable power.

EXPERIMENTS ON THE BILIARY SECRETION OF THE DOG. By Prof. RUTHERFORD, assisted by W. J. DODDS, M.B., D.Sc.

FOURTH SERIES.

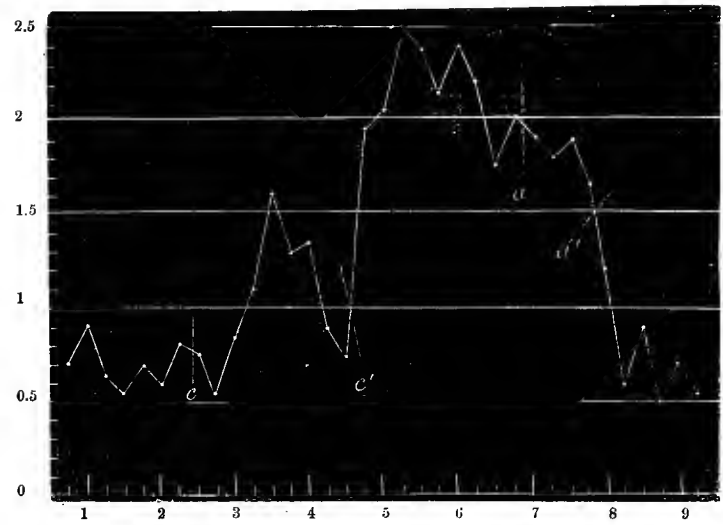
ACTION OF PHYSOSTIGMA.

SINCE the well-known researches of Sir Robert Christison and Professor Fraser, the physiological actions of Calabar bean have been made the subject of extensive inquiry; its action on the liver has not, however, hitherto been investigated, owing to the want of a reliable method of experiment. As stated by Professor Fraser, this agent excites the salivary, intestinal, and lachrymal glands; and at his request we performed the following experiments on the liver. The extract of Calabar bean of the *British Pharmacopœia* was the preparation employed, the maximum dose of which for the human subject is a quarter of a grain.

Experiment 61. Dog that had fasted 18 hours. Weight 26.7 kilogrammes (Fig. 61).—1 grain extract of Calabar bean triturated with half cc. of bile, half cc. of rectified spirit, and 5 cc. of water, was injected into the duodenum at *c*, and the same dose was given again at *c'*. The increased secretion of bile was decided and prolonged after the second dose. The bile and alcohol were employed merely to promote absorption of the active principle; and it may be safely assumed that none of the effect was directly due to either, for it has been already stated that 2 cc. or 3 cc. of bile introduced into the duodenum does not notably affect the biliary secretion; and it will be shown that a much larger quantity of alcohol than was given in this case has also no effect (Experiments 74A and 74B).

Although the antagonism between the atropia and physostigma has been abundantly proved by Fraser, Arnstein, Heidenhain, and others, it was nevertheless deemed desirable to definitely ascertain whether or not, in the case of the liver, this antagonism also obtains; accordingly, four-fifths of a grain of atropia sulphate, dissolved in 3 cc. of water, was injected into the duodenum at *a*. The effect being somewhat doubtful, three-fifths of a grain dissolved in 3 cc. of water was injected into the

Fig. 61.



Secretion of bile before and after Calabar bean and atropia. 1 grain extract Calabar bean with $\frac{1}{2}$ cc. bile, $\frac{1}{2}$ cc. rectified spirit, and 5 cc. water, injected into duodenum at c, and again at c'; $\frac{4}{5}$ths grain atropia sulphate injected into duodenum at a; $\frac{3}{5}$ths grain into jugular vein at a'.

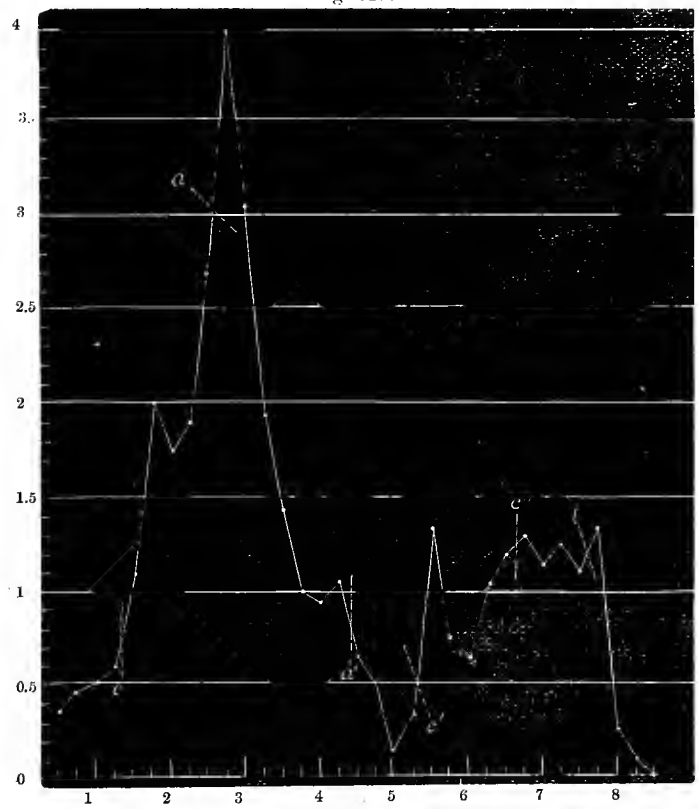
Experiment 61.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
0.70		2.50	
0.90		2.40	
0.65		2.15	0.365 cc.
0.55		2.40	
0.70	0.098 cc.	2.20	
0.60		1.75	
0.80		2.00	
c ——		a ——	
0·75		1.90	
0.55		1.80	
0.85		1.90	
1.10		1.65	
1.60		a' ——	
1.30		1.20	
1.35		0.60	
0.90		0.90	
0.75		0.50	0.098 cc.
c' ——		0.70	
1.95		0.55	
2.05			

jugular vein. The bile-secretion speedily fell, and it is evident from the chart that within half an hour after the administration of the second dose the effect of the physostigma had entirely disappeared.

NECROPSY. — There was decided irritation of the duodenal

Fig. 61A.



Secretion of bile before and after Calabar bean, atropia, and lead acetate. 2 grains extract of Calabar bean with 1 cc. of bile and 5 cc. of water injected into the duodenum at *c*; 1½ grain extract, with same, at *c'*; 2 grains extract, with same, at *c''*; ⅙ths of a grain of atropia sulphate in 4 cc. of water injected into the jugular vein at *a*; ⅙ths of a grain at *a'*; 8 grains of lead acetate in 20 cc. of water injected into the duodenum at *l*.

mucous membrane to the extent of 8 inches below the pylorus. Evidence of only slight purgative action was found in the small intestine.

Experiment 61A. Dog that had fasted 18 hours. Weight

13.6 kilogrammes (Fig. 61A).—Two grains of the extract of Calabar bean, triturated with 1 cc. bile and 5 cc. water, were injected into the duodenum at *c*. The stimulating effect on the

Experiment 61A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
0.35	} 0.138 cc.	0.65	} 0.121 cc.
0.45		0.50	
0.50		0.15	
0.60		0.35	
c ——		*c′* ——	
1.10		1.35	
2.00		0.85	
1.75		0.75	
1.90	} 0.753 cc.	1.05	
2.70		1.10	
a ——		*c″* ——	
4.00		1.30	
3.05		1.15	
1.95		1.25	
1.45		1.10	
1.00		*l* ——	
0.95		1.35	
1.05		0.25	
a′ ——		0.00	

liver was rapid and very powerful. Four-fifths of a grain of atropia sulphate, dissolved in 4 cc. water, was injected into the jugular vein at *a*. This was done just five minutes before the next reading of the bile. It is, therefore, certain that much of the bile that formed the highest reading in the experiment was secreted previous to the injection of the atropia; and, as atropia did not increase the secretion in the preceding experiment, it follows that the very high reading of the bile immediately subsequent to the atropia administration is to be attributed to the action of the physostigma not yet antagonised. Ere long, however, the atropia asserted its influence and antagonised the physostigma. At *a′*, three-fifths of a grain of atropia sulphate was again injected into the jugular vein, and it is evident from the chart that the physostigma was completely antagonised thereby. A continuation of the experiment was, perhaps,

scarcely necessary; still a grain and a half of Calabar extract triturated with 1 cc. bile and 5 cc. water, was injected into the duodenum at *c'*, and two grains of the extract similarly treated were injected at *c''*. The exciting effect was not very marked; nor need this be wondered at, considering how powerfully the liver had been previously stimulated, and its partial exhaustion induced not merely owing to the above cause, but also owing to the duration of the experiment.

As the action of acetate of lead on the liver was to be investigated, eight grains of that substance, dissolved in 20 cc. of water, were injected into the duodenum at *l*, and the secretion of bile soon thereafter came to a standstill. Subsequent experiments show that this effect was unusual and attributable to the depressant effect of the lead on a liver already well-nigh exhausted.

NECROPSY.—Great irritation of the mucous membrane of the small intestine to the extent of about fifteen inches below the pylorus. The viscus contained only slight evidence of purgative action.

Result of Experiment with Physostigma.—The relation of the dose to the size of the animal, and the coefficients of the secretion before and after its administration, are stated in Table XIX.

TABLE XIX.

Physostigma.	Total Dose in Grains.	Grains per Kilogramme of Body-weight.	Secretion of Bile per Kilogramme of Body-weight per hour.	
			Before.	After.
Experiment 61, .	2 with bile	0.0074	0.098 cc.	0.365 cc.
Experiment 61A, .	2 ,,	0.0147	0.138 cc.	0.753 cc.

It is interesting to observe that in Experiment 61A the dose, which, in relation to the size of the animal, was twice as great as in Experiment 61, raised the coefficient of secretion to a little more than twice the figure attained in Experiment 61, showing

forcibly the precision of the experimental method employed. The high coefficient in Experiment 61A indicates a very powerful effect; yet, since the dose employed was four times the maximum dose for a man, and seeing that one grain produced only a trifling effect in Experiment 61, it may be inferred that, in the human subject, physostigma will probably be found to have, in the relatively small doses administered, an insignificant effect on the liver; for many of the preceding experiments have demonstrated that, when the same dose of a substance that powerfully excites the human liver is given to an average-sized dog, it powerfully excites its liver. It is an error to suppose that the dog requires much larger doses of all drugs than are necessary for the human subject. The effect of physostigma on the liver is completely antagonised by atropia sulphate.

Prevost of Geneva, in a communication to the Paris Academy of Sciences (August 3, 1874), states that muscaria increases the biliary secretion, and that atropia checks the hypersecretion due to muscaria.

Action of Atropia.

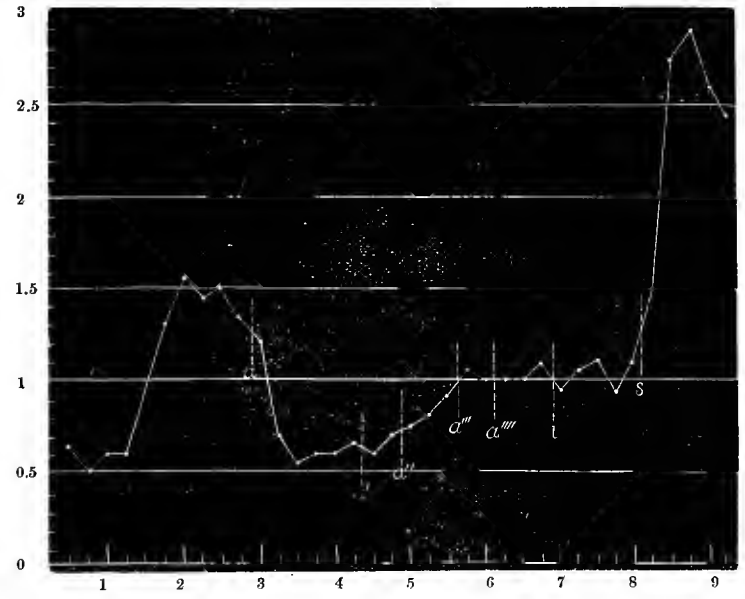
It is known that atropia causes purgation and diuresis in dogs (*Op.* viii. p. 322). On the other hand, it paralyses the chorda tympani and the secretory nerves of the sweat and milk glands, and thereby arrests their secretions. It therefore seemed desirable to give atropia previous to the administration of any other substance, in order to determine its influence on the liver.

Experiment 62. Dog that had fasted 18 hours. Weight 16.1 kilogrammes (Fig 62).—In this experiment the secretion of bile rose at the end of the first hour, although no drug had been administered. Our previous experiments have convinced us that this is due to reaction, which is apt to ensue unless great care is taken to pull as little as possible at the bile-duct during the operation for inserting the cannula.

Half a grain of atropia sulphate, dissolved in twenty minims of water, was injected into the jugular vein at a, a', a'', and a'''; and one grain was injected at a''''. Thus three grains were given in all. The fall of secretion after the first dose may be

discarded, as it would probably have taken place had no atropia been given. It is evident that the atropia does not arrest the secretion of bile as it does that of saliva, sweat, and milk. Nor

Fig. 62.



Secretion of bile before and after atropia sulphate, lead acetate, and sodium salicylate. ½ grain of atropia sulphate in 20 minims of water injected into jugular vein at a, a', a'', and a'''; 1 grain injected into vein at a''''; 10 grains of lead acetate in 20 cc. of warm water injected into the duodenum at l; 25 grains of sodium salicylate in 25 cc. of water injected into the duodenum at s.

can it be said to augment it; for the increased secretion that followed the third dose is trivial, and may be discarded in view of the sequel to the second dose in Experiment 61A.

Ten grains of acetate of lead, dissolved in 20 cc. of tepid water, were injected into the duodenum at l, without producing any notable effect.

Having, in other experiments—mentioned in the sequel—discovered that the alkaline salts of benzoic acid are powerful hepatic stimulants, I suspected that the alkaline salts of salicylic acid would be found to have a similar action. Accordingly, twenty-five grains of sodium salicylate, dissolved in 25 cc. of

water, were injected into the duodenum, and within half an hour a very rapid secretion of bile had begun; and this, notwith-

Experiment 62.

Secretion of bile per 15.″	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.65		0.75	
0.50		0.80	
0.60		0.90	
0.60		a''' ——	
1.00		1.05	
1.30		1.00	
1.55		a'''' ——	
1.45		1.00	
1.50		1.00	
1.35		1.10	
a ——		l ——	
1.20		0.95	
0.70		1.05	
0.55		1.10	0.260 cc.
0.60		0.95	
0.60		1.10	
0.65		s ——	
a' ——		1.50	
0.60		2.75	
0.70		2.90	0.664 cc.
a'' ——		2.60	
		2.45	

standing the previous administration of lead acetate and three grains of atropia sulphate.

Result of Experiments with Atropia—Atropia sulphate does not paralyse the hepatic cells, neither does it appear to excite them. Whether or not it possesses the power of paralysing the hepatic secretory nerves is doubtful; but, seeing that it antagonises the effect of physostigma on the liver, and remembering the actions of these substances on the nerves of the heart and salivary glands, the suspicion is entertainable that physostigma stimulates the hepatic cells through a nervous apparatus that is affected in an opposite sense—possibly paralysed—by atropia; while the hepatic cells, and perhaps some nervous mechanism like the motor ganglia of the heart in close relation to them, are unaffected by atropia.

Action of Resina Menispermi or "Menispermin."

The substance termed menispermin by Keith & Co. of 41 Liberty Street, New York, is derived from the root of the yellow parilla (*Menispermum canadense*). Messrs Keith have informed me that the crude root of the plant is dried, crushed, and percolated with alcohol. The alcohol is then evaporated or distilled off, leaving the active principles in the form of an extract, which is then "freed from impurities," dried, and pulverised. How it is *freed from impurities* is not stated. This is also the manner in which they prepare baptisin, phytolaccin, hydrastin, and juglandin—substances whose actions are described in the sequel.

Menispermin is stated by Keith (*Op.* xiv.) to be "alterative, tonic, laxative, diuretic, stimulant, and resolvent, and to be useful in hepatic torpor, indigestion," &c. On this account, we experimented with it on the liver; but we probably would not

Experiment 63.

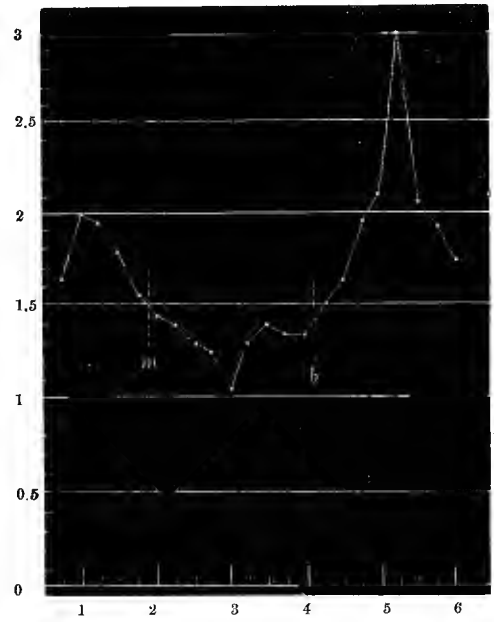
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.65		1.40	0.233 cc.
2.00		1.35	
1.95	0.311 cc.	1.35	
1.80		*b* ——	
1.55		1.50	
m ——		1.65	
1.45		1.95	
1.40		2.10	0.394 cc.
1.30		3.00	
1.25		2.05	
1.05		1.95	
1.30	0.233 cc.	1.75	

have taken the trouble had we at the time been aware of the account given of its effects by Wood and Bache (*Op.* x. p. 1555). In that account the root is said to be a gently stimulating tonic, probably very closely allied to calumba, which also belongs to the Menispermaceæ. The medium dose of Keith's menispermin for a man is two grains.

Experiment 63. Dog that had fasted 18 hours. Weight

23.1 kilogrammes (Fig. 63).—Seven grains of menispermin, triturated with 1.5 cc. of bile and 3 cc. of water, were injected

Fig. 63.



Secretion of bile before and after menispermin and baptisin. 7 grains of menispermin in 1·5 cc. of bile and 3 cc. of water injected into the duodenum at *m*; 7 grains of baptisin in 2 cc. of bile and 3 cc. of water injected at *b*.

into the duodenum at *m*; and, as no obvious effect ensued, seven grains of baptisin, similarly treated, were injected into the duodenum at *b*. The secretion of bile thereafter speedily rose. The result was evidently somewhat equivocal, and therefore another experiment, in which menispermin was alone given, was performed.

Necropsy.—The duodenal mucous membrane showed only one slightly reddened patch. There was but scanty evidence of purgative action, for the upper part of the small intestine contained only 35 cc. of fluid; but whether due to a purgative action of the menispermin, or of the baptisin, could not be apparent from this experiment.

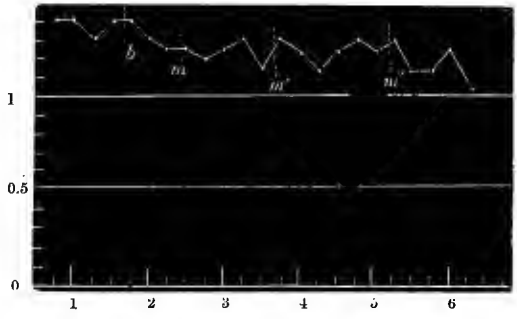
Experiment 63A. Dog that had fasted 17 hours. Weight 15.7 kilogrammes (Fig. 63A).—Two cc. of bile and 2 cc.

Experiment 63A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
1.4		*m′* ——	
1.4		1.30	
1.3		1.25	
1.4		1.15	
b ——		1.25	
1.4	0.34 cc.	1.30	0.315 cc.
1.3		1.25	
1.25		*m″* ——	
m ——		1.30	
1.25		1 15	
1.20		1.16	
1.25		1.25	0.287 cc.
1.30		1.05	
1.15		1.05	

of water were injected into the duodenum at *b*. This producing no perceptible effect on the secretion, five grains of menispermin

Fig. 63A.



Secretion of bile before and after menispermin. 2 cc. of bile and water injected into the duodenum at *b* ; the same, with 5 grains of menispermin, injected at *m*, and again at *m′* ; the same, with 10 grains injected at *m″*.

were triturated with the same amount of bile and water, and injected into the duodenum at *m* ; and the same dose was

repeated at *m'*. The secretion remaining unaffected, ten grains with bile and water, as before, were injected at *m''*. The bile-secretion was remarkably constant, and the experiment clearly proved that this substance, even in large doses, does not excite the liver; and that the rise of secretion observed in Experiment 63 could not be ascribed to the menispermin. Indeed, the chart of this experiment (Fig. 63A) simply shows the normal curve of bile-secretion in a fasting animal.

NECROPSY.—The mucous membrane of the upper third of the small intestine was slightly reddened, and there was evidence of decided purgative action; for, while only 16 cc. of fluid had been injected, the small intestine contained 170 cc. of yellowish fluid containing much mucus.

Result of Experiments with Menispermin.—This substance is an intestinal, but not a hepatic, stimulant.

ACTION OF RESINA BAPTISIÆ OR "BAPTISIN."

The substance termed "baptisin" is an impure resin prepared from the root of the wild indigo plant (*Baptisia tinctoria*) after the same manner as menispermin. The specimen employed in these experiments was obtained from Keith & Co. of New York. The root of this plant is said to be a powerful emetic and cathartic in large, and a mild laxative in small, doses. Stevens of Pennsylvania recommends a decoction of the root in epidemic dysentery. It is said to have proved useful in scarlatina, typhus fever, and in that state of the system that attends mortification (*Op.* x. p. 1469). The physiological actions of this plant have apparently not been investigated, and it is nowhere stated that it is a cholagogue. The dose of baptisin for a man is from one to five grains.

In Experiment 63 it has already been shown that baptisin increases the biliary secretion; but, as in that experiment its administration followed that of menispermin, it was desirable to give baptisin first in another experiment.

Experiment 64. Dog that had fasted 17 hours. Weight 18.7 kilogrammes (Fig. 64).—Seven grains of baptisin triturated with 2 cc. of bile and 5 cc. of water were injected into the duo-

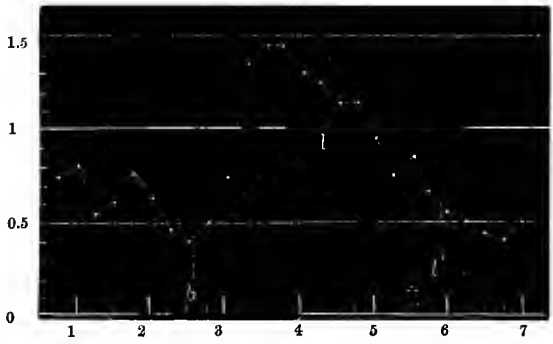
denum at *b*. In half an hour its stimulating effect on the liver was perceptible, and in the course of an hour it became very evident.

Experiment 64.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.75		1.30	0.296 cc.
0.80		1.25	
0.55		*l* ——	
0.60		1.15	
0.75		1.15	
0.65	0.120 cc.	0.95	
0.45		0.75	
0.40		0.85	
b ——		0.65	
0.45		*l′* ——	
0.50		0.55	
0.75		0.50	
1.35		0.45	0.098 cc.
1.45	0.296 cc.	0.40	
1.45		0.50	

As this result confirmed the observation made in Experiment 63 no more baptisin was given.

Fig. 64.



Secretion of bile before and after baptisin and lead acetate. 7 grains of baptisin, with 2 cc. of bile and 5 cc. of water, injected into the duodenum at *b*; 8 grains of lead acetate in 15 cc. of water injected at *l*; 12 grains in 25 cc. of warm water at *l′*.

With a view to follow up the observations made with lead acetate in Experiments 61A and 62, eight grains of lead acetate

dissolved in 15 cc. of water were injected into the duodenum at *l*, and 12 grains of the same in 25 cc. of tepid water were injected at *l'* into the lower part of the small intestine. The result was equivocal, in so far as the secretion of bile would doubtless have diminished had no lead been given. The experiment is, therefore, decisive as regards the action of baptisin, but inconclusive as regards that of lead.

Necropsy.—Considerable redness of the mucous membrane of about 15 inches of upper part of small intestine. Slight evidence of purgative action.

Result of Experiments with Baptisin.—The two experiments with this substance prove it to be a hepatic stimulant, and Table XX. indicates its power as such.

Table XX.

Baptisin.	Total Dose in Grains.	Grains per Kilogramme of Body-weight.	Secretion of Bile per Kilogramme of Body-weight per hour.	
			Before.	After.
Experiment 63, .	7 with bile,	0.303	0.233 cc.	0.394 cc.
Experiment 64, .	7 ,,	0.374	0.120 cc.	0.296 cc.

Taking into account the fact that in Experiment 64 the coefficient of bile-secretion did not rise higher than 0.296 cc., when nothing but baptisin had been administered, and at the same time the dose being relatively larger than in Experiment 63, it may be concluded that this substance is a hepatic and also an intestinal stimulant of moderate power, and it may possibly be found of service as a hepatic stimulant in cases of torpid liver with a depressed condition of the system tending to gangrene. We commend it to the attention of the physician.

Action of Resina Phytolaccæ or "Phytolaccin."

The poke-plant (*Phytolacca decandra*) grows abundantly in the United States. The root is the part employed; and in small

doses it is said to act as an alterative, and has been highly recommended in chronic rheumatism. In large doses it produces excessive vomiting and purging, with great prostration of strength, and sometimes with convulsions (*Op.* x. p. 646). The preparation employed by us was a substance termed "phytolaccin," prepared from the root of the plant by Keith & Co. of New York, after the same manner as menispermin (p. 97). The dose for a man is from one to three grains. The physiological actions of the phytolacca have not hitherto been investigated.

Experiment 65. Dog that had fasted 18 hours. Weight

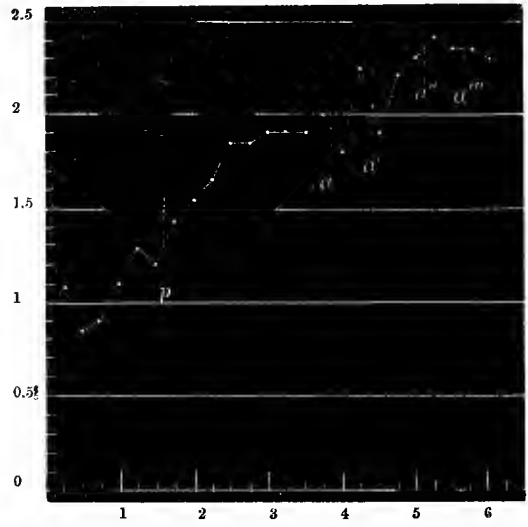
Experiment 65.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.10		2.00	0.244 cc.
0.85		*a* ——	
0.90		1.80	
1.10		2.25	
1.30	0.144 cc.	*a′* ——	
1.20		1.90	
p ——		2.20	
1.45		2.30	
1.55		*a″* ——	
1.65		2.40	
1.85		2.35	0.299 cc.
1.85		*a‴* ——	
1.90		2.35	
1.90	0.244 cc.	2.30	
1.90			

31.1 kilogrammes (Fig. 65.)—Two grains of phytolaccin triturated with 2 cc. of bile and 4 cc. of water were injected into the duodenum at *p*. The subsequent excitement of the liver was unequivocal. When the increase of secretion was well declared, one-tenth of a grain of atropia sulphate dissolved in ten minims of water was injected into the jugular vein at *a*, and again at *a′*, *a″*, *a‴*—in all four-tenths of a grain; but the stimulating effect of the phytolaccin was not antagonised thereby. Had this experiment been performed after instead of before Experiment 61, a larger dose of atropia would have been given. Remember-

ing the non-exciting effect of atropia on the liver, the high secretion at the close of the experiment may be safely referred to the continued action of the phytolaccin.

Fig. 65.



Secretion of bile before and after phytolaccin and atropia. 2 grains of phytolaccin in 2 cc. of bile and 4 cc. of water injected into the duodenum at *p*; 1-10th of a grain of atropia sulphate injected into the jugular vein at *a*, *a'*, *a''*, and *a'''*.

NECROPSY.—The duodenal mucous membrane was slightly reddened, but there was no evidence of purgative action worthy of mention.

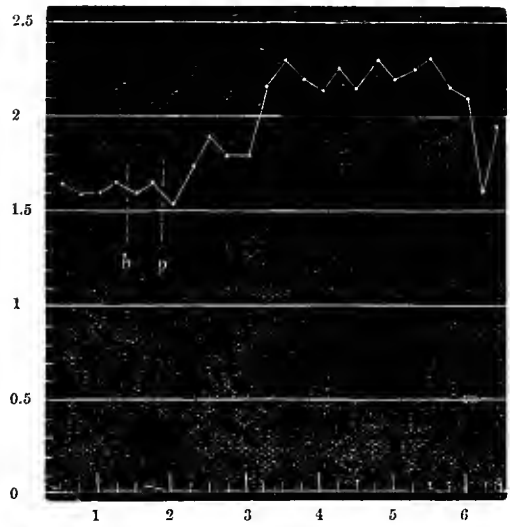
Experiment 65A. Dog that had fasted 17 hours. Weight 19.2 kilogrammes (Fig. 65A).—Two cc. of bile and 2 cc. of water were injected into the duodenum at *b*, and 2 grains of phytolaccin triturated with the same fluids were injected at *p*. A considerable increase of bile-secretion ensued. Owing to the high secretion previous to the administration of the drug, the result is less striking than in the preceding experiment; yet, in this case the coefficient of secretion was much higher than in the former experiment (Table XXI), a circumstance which was probably largely due to the fact that, while the same dose was given in both cases, the subject of Experiment 65A was much smaller

than that of Experiment 65. The liver of dog 65A was, therefore, more powerfully affected than that of dog 65.

Experiment 65A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
1.65		2.30	
1.60		2.20	
1.60		2.15	
1.65		2.25	
b ——	0.338 cc.	2.15	
1.60		2.30	
1.65		2.20	0.471 cc.
p ——		2.25	
1.55		2.30	
1.75		2.15	
1.90		2.10	
1.80		1.60	
1.80		1.95	
2.15			

Fig. 65A.



Secretion of bile before and after phytolaccin. 2 cc. of bile and 2 cc. of water injected into the duodenum at *b*; 2 grains of phytolaccin with 2 cc. of bile and 2 cc. of water injected at *p*.

NECROPSY.—The small intestine contained 40 cc. of liquid, indicating a mild purgative effect.

Result of Experiments with Phytolaccin.—It is a mild intestinal, but a powerful hepatic, stimulant, as is shown by Table XXI.

TABLE XXI.

Phytolaccin.	Total Dose in Grains.	Grains per kilogramme of Body-weight.	Secretion of Bile per kilogramme of Body-weight per hour.	
			Before.	After.
Experiment 65, .	2 with bile,	0.064	0.144 cc.	0.299 cc.
Experiment 65A, .	2 ,,	0.104	0.338 cc.	0.471 cc.

Considering the small dose that was given, the high coefficient of secretion in Experiment 65A is probably to be regarded as a nearer indication than that in Experiment 65 of the power of phytolaccin as a hepatic stimulant. This substance appears to be eminently worthy of the attention of the physician.

ACTION OF RESINA HYDRASTIS OR "HYDRASTIN."

The root of the *Hydrastis canadensis* has had various medicinal properties claimed for it. It is admitted by all to be tonic, and by some it is said to be aperient, cholagogue, diuretic, antiseptic, &c. "It has been employed in dyspepsia and other affections requiring tonic treatment, in jaundice and other functional disorders of the liver, as a laxative in constipation and hæmorrhoids, and as an alterative in various diseases of the mucous membranes, such as catarrh, chronic enteritis, &c. By some it is used as one of the best substitutes for quinia in intermittents." These and other statements regarding it are made by Wood and Bache (*Op.* x. p. 458), who further aver that a "more precise investigation of its physiological and therapeutic properties is necessary before we can venture to decide its place among medicines." It contains an alkaloid, hydrastia or hydrastin, which has been found to be identical with berberina (*Op.* x. p. 457), found in the *Berberis vulgaris* and in calumba. The "hydrastin"

employed in the following experiments was not the alkaloid, but a resinous substance prepared from the root of the plant, in the same manner as menisperim (p. 97) by Keith & Co. of New York. The dose for a man of this preparation is from one to two grains.

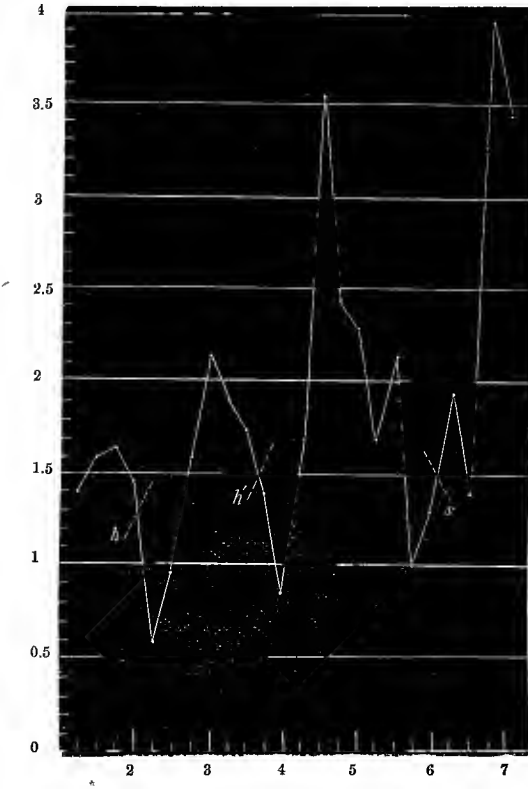
Experiment 66. Dog that had fasted 17 hours. Weight

Experiment 66.		Experiment 66A.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.40		0.7	
1.60	0.230 cc.	0.35	
1.65		0.60	
1.45		0.35	
h ——		0.30	
0.60		0.40	
0.95		0.30	0.09 cc.
1.60		0.35	
2.15		*h* ——	
1.90		0.17	
1.75		0.17	
h′——		0.15	
1.40		0.10	
0.85		0.30	
1.70		0.20	
3.55		0.15	
2.45	0.386 cc.	0.30	
2.30		0.35	
1.70		0.55	
2.15		*h′*——	
1.00		0.60	
1.30		0.80	
s ——		0.80	
1.95		0.90	
1.40		1.10	0.323 cc
3.95		1.15	
3.45		1.05	
		1.10	
		0.95	
		1.05	

25.9 kilogrammes (Fig. 66).—Two grains of hydrastin triturated with 2 cc. of rectified spirit, 1 cc. of bile, and 2 cc. of water were injected into the duodenum at *h*, and the same dose was repeated at *h′*. A wave, as it were, of increased bile-secretion followed both doses, the second being higher than the first. It

is notable that the periods of excitement after both doses were of the same length—an hour and a half. Twenty grains of sodium salicylate in 10 cc. of water were then injected into a

Fig. 66.



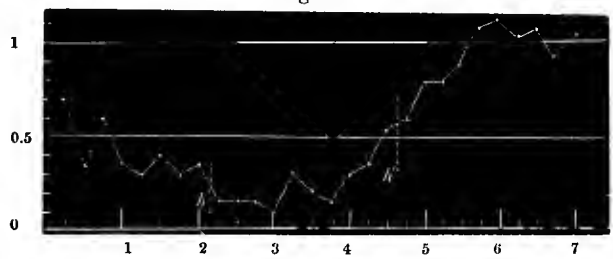
Secretion of bile before and after hydrastin and sodium salicylate. 2 grains of hydrastin in 2 cc. of rectified spirit, 1 cc. of bile, and 2 cc. of water injected into the duodenum at *h* and *h'*; 20 grains of sodium salicylate in 10 cc. of water injected into the lower portion of the intestine at *s*.

lower part of the small intestine (*s*), and it produced a higher bile-secretion than had resulted from the hydrastin.

NECROPSY.—Decided redness of mucous membrane in the upper 12 inches of the small intestine; but there was only scanty evidence of purgation where the hydrastin had been injected.

Experiment 66A. Dog that had fasted 17 hours. Weight 13.6 kilogrammes (Fig. 66A).—Two grains of hydrastin,

Fig. 66A.



Secretion of bile before and after hydrastin. 2 grains of hydrastin in 2 cc. of bile, 1 cc. of rectified spirit, and 6 cc. of water injected into the duodenum at *h* and *h'*.

triturated with 2 cc. of bile, 1 cc. of rectified spirit, and 6 cc. of water, were injected into the duodenum at *h*, and the same dose was again given at *h'*. Before the experiment was begun, it was observed that the animal was somewhat unhealthy, which accounts for the result being less definite in this than in the previous case: yet, ere the second dose was given, the bile-secretion had begun to rise, and after the second dose the increase was decided.

NECROPSY.—Slightly increased redness of duodenal mucous membrane. Very slight evidence of purgative action.

Result of Experiments with Hydrastin. — It is a hepatic

TABLE XXII.

Hydrastin.	Total Dose in Grains.	Grains per kilogramme of Body-weight.	Secretion of Bile per kilogramme of Body-weight per Hour.	
			Before.	After.
Experiment 66, .	2 with bile,	0.077	0.23 cc.	0.386 cc.
Experiment 66A, .	2 ,,	0.147	0.09 cc.	0.323 cc.

stimulant of considerable power, and a feeble intestinal stimulant. The fact shown in Table XXII. that in Experiment 66A a dose relatively larger in proportion to the size of the animal

than in Experiment 66 produced a smaller effect on the liver—seems only explicable by the fact that the subject of the former experiment was, as already stated, in an abnormal condition. Altogether, hydrastin appears to be a substance eminently worthy of the attention of the physician.

Action of Resina Juglandis or "Juglandin."

The juglandin employed in the following experiment was not an alkaloid, but an impure resin prepared by Keith & Co. of New York, from the bark of the root of the butternut or white walnut (*Juglans cinerea*), after the same manner as menispermin (p. 97). Regarding the properties of the bark of the butternut, Wood and Bache (*Op.* x. p. 492) state that it is a mild cathartic, operating without pain or irritation, and resembling rhubarb in the property of evacuating without debilitating the alimentary canal. It was much employed during the late American civil war by Dr Rush and other army physicians. It is especially useful in habitual costiveness and dysentery. Nothing is stated regarding any influence on the liver. An extract of the bark is officinal in the United States. The dose of Keith's juglandin—the substance used in the following experiment—is from two to five grains.

Experiment 67. Dog that had fasted 18 hours. Weight 21.1 kilogrammes (Fig. 67).—Five grains of juglandin, triturated with 2 cc. of bile, 2 cc. of rectified spirit, and 5 cc. of water, were injected into the duodenum at *j*, and the same dose was repeated at *j'*. Both doses were followed by increased bile-secretion, which lasted four hours, and would probably have lasted even longer. Twenty grains of sodium salicylate in 10 cc. of water were injected into a lower part of the small intestine at *s*, and speedily caused a much greater hepatic excitement. Before any drug was given, the coefficient of secretion was 0.104 cc. of bile per kilogramme of body-weight per hour. After the first dose, it rose to 0.286 cc. and after the second to 0.327, showing that juglandin is a hepatic stimulant of moderate power. Indeed, it occasions a coefficient of secretion almost precisely the same as rhubarb (0.32 cc.) and leptandria (0.31 cc.).

NECROPSY.—Slightly increased redness of the duodenum, and slight purgation.

Experiment 67.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.75		1.30	
0.65		*j* ——	
0.45		1.45	
0.45		1.75	
0.40		1.65	
0.45		1.65	0.327 cc.
0.45	0.104 cc	1.85	
0.45		1.55	
0.65		1.60	
0.65		1.70	
j ——		1.65	
0.60		*s* ——	
0.85		1.95	
0.95		3.40	
1.80		3.75	
1.40	0.286 cc.		
1.55			
1.30			

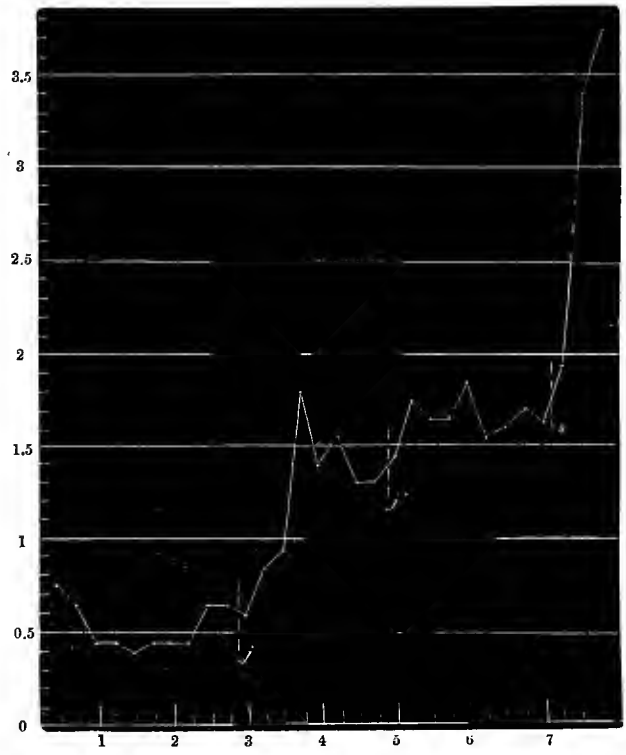
Result of Experiment with Juglandin.—It is a mild hepatic stimulant and a mild purgative, and seems eminently worthy of the attention of the physicians of this country.

ACTION OF BENZOIC ACID AND ITS COMPOUNDS.

Benzoic acid is said to act as a stimulant of the system generally, and particularly of the kidneys, mucous membrane of the bladder, and bronchial glands. It is nowhere stated to be a cholagogue. Yet it is sometimes used empirically in hepatic affections. Tanner, in his *Practice of Medicine*, recommends ammonium benzoate in hepatic congestion with deficient urine, and benzoic acid in suppressed action of the liver and uræmia. Dr Wade of Birmingham employs benzoic acid in cases of catarrh of the bile-ducts; and we owe to the deep interest which he has taken in this research the valuable suggestion that we should endeavour to furnish a rational theory for the use of

this agent in hepatic affections, by ascertaining whether or not it has the power of stimulating the liver. For a man, the dose

Fig. 67.



Secretion of bile before and after juglandin and sodium salicylate. 5 grains of juglandin in 2 cc. of rectified spirit, 2 cc. of bile, and 5 cc. of water injected into the duodenum at *j* and *j'*; 20 grains of sodium salicylate in 10 cc. of water injected into the lower portion of the intestine at *s*.

of benzoic acid is from ten to thirty grains; that of benzoate of ammonia, from ten to twenty grains. Benzoate of soda has been employed by Socquet and Bonjean (Wood and Bache *Op.* x. p. 1471) as a remedy for gout and rheumatism; but we have not been able to ascertain the dose given. Probably the dose of the sodium is similar to that of the ammonium salt.

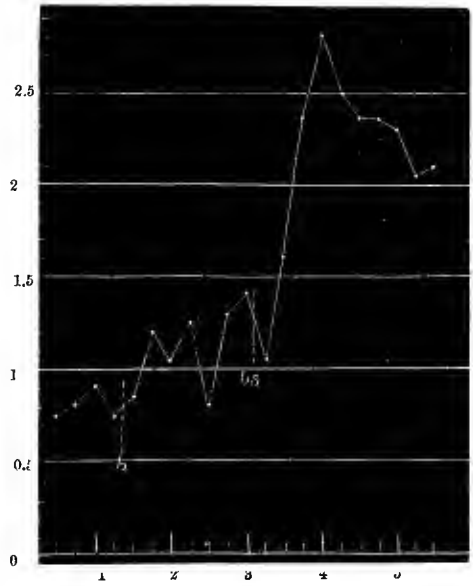
Experiment 68. Dog that had fasted 17 hours. Weight 14.3 kilogrammes (Fig. 68).—Fifteen grains of benzoic acid, partially dissolved in 20 cc. of water, were injected into

the duodenum at *b*. A slight increase of the bile-secretion ensued; but it was not thought judicious to repeat the benzoic

Experiment 68.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.75		*bs* —	
0.80	0.223 cc.	1.05	
0.90		1.60	
0.75		2.35	
b —		2.80	
0.85		2.50	
1.20		2.35	0.646 cc.
1.05		2.35	
1.25		2.05	
0.80	0.332 cc.	2.10	
1.30			
1.40			

Fig. 68.



Secretion of bile before and after benzoic acid and sodium benzoate. 15 grains of benzoic acid in 20 cc. of water injected into the duodenum at *b*; 20 grains of sodium benzoate in 10 cc. of water injected at *bs*.

acid, owing to the fallacy that would have arisen from the effect of the large quantity of water required for its solution. Accordingly, twenty grains of sodium benzoate—an extremely soluble substance—dissolved in 10 cc. of water, were injected at *bs*, and a very powerful stimulation of the liver was the result, the coefficient of secretion rising as high as 0·646 cc. of bile per kilogramme of body-weight per hour.

NECROPSY.—Very slight increase of redness of the duodenal mucous membrane. No purgation.

Experiment 68A. Dog that had fasted 18 hours. Weight

Experiment 68A.

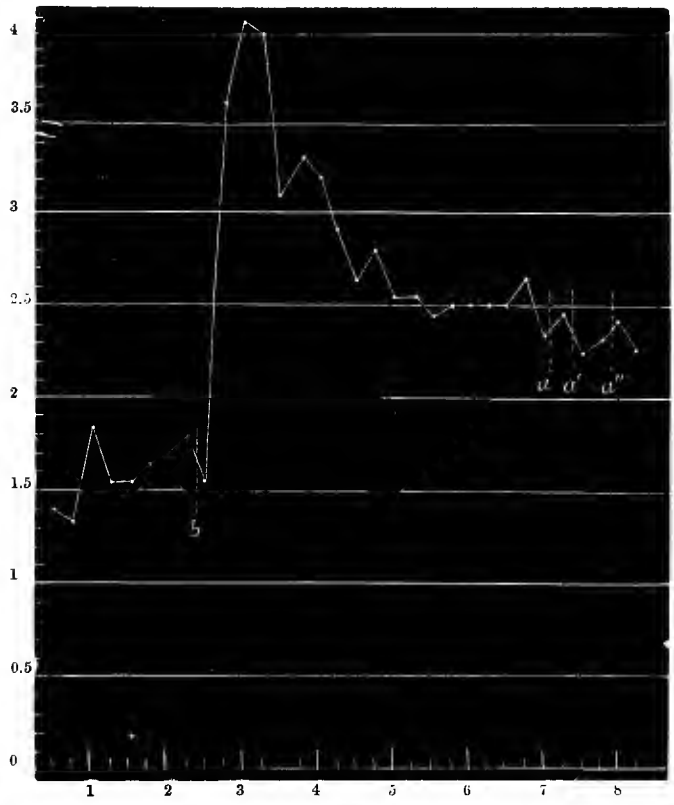
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.40		2.80	
1.35		2.55	
1.85		2.55	
1.55		2.45	
1.55		2.50	
1.65	0.247 cc.	2.50	0.37 cc.
1.70		2.50	
1.80		2.50	
b ——		2.65	
1.55		2.35	
3.63		*a* ——	
4.05	0.544 cc.	2.45	
4.00		*a′* ——	
3.10		2.25	
3.30		2.30	
3.20		*a″* ——	
2.90		2.40	
2.65		2.25	

27.1 kilogrammes (Fig. 68A).—Twenty grains of ammonium benzoate, dissolved in 25 cc. of water, were injected into the duodenum at *b*. Within half an hour a powerful stimulation of the liver ensued that lasted five hours, and would probably have continued still longer had the experiment been continued. One-fifth of a grain of atropia sulphate, injected into the jugular vein at *a*, *a′*, and *a″*—three-fifths of a grain in all—did not antagonise the action of the benzoate.

NECROPSY.—There was no purgation, the intestine being

perfectly dry; but the mucous membrane of the small intestine was considerably reddened to the extent of 3 feet below the pylorus.

Fig. 68A.



Secretion of bile before and after ammonium benzoate and atropia. 20 grains of ammonium benzoate in 25 cc. of water injected into the duodenum at *b*; one-fifth of a grain of atropia sulphate injected into the jugular vein at *a*, *a'*, and *a''*.

A repetition of experiments so entirely satisfactory was unnecessary; nevertheless, in Experiment 72A there was a reason for giving sodium benzoate, and hepatic excitement again resulted from it.

TABLE XXIII.

	Total Dose in Grains.	Grains per kilogramme of Body-weight.	Secretion of Bile per kilogramme of Body-weight per hour.	
			Before.	After.
Sod. benzoate.—Ex. 68,	20	1.320	0.223 cc.	0.646 cc.
Ammon. ,, ,, 68A,	20	0.737	0.247 cc.	0.544 cc.

Result of Experiments with the Benzoates.—Sodium benzoate and ammonium benzoate are both very powerful stimulants of the liver, but are not stimulants of the intestinal glands. It appears from the above experiments that the salt of sodium is a more powerful stimulant than that of ammonium; but the experiments are inconclusive on this point, because in Experiment 68 the sodium salt was assisted in its action by the previous administration of benzoic acid, and in addition the dose of the salt was greater in proportion to the size of the animal than in Experiment 68A. Now that we have proved this action of these substances on the liver of the dog, a similar action on the human liver will doubtless be found; and probably the reason why it has hitherto escaped the attention of physicians is, that these substances, being hepatic but not intestinal stimulants, the hypersecretion of bile induced by them has not been revealed so as to attract attention. But probably, if a dose of sodium or ammonium benzoate were given at night, and a purely intestinal stimulant, such as magnesium sulphate, given in the morning, clear evidence would be found of the increased secretion of bile. These results, therefore, furnish a rational theory for the employment of the benzoates in congestion and some other affections of the liver. In view of the above discovery, we would ask the practical physician to consider the propriety of testing the effect of the benzoates in dysentery, for while they, like ipecacuan, powerfully stimulate the liver, and not the intestinal glands, they, unlike ipecacuan, induce no sickness or depression, but on the contrary, are nerve stimulants.

Both the sodium and ammonium salts should be tried. It may also be well to observe that it would be perhaps advisable to more frequently administer the benzoates in ordinary bronchial catarrh, for they stimulate the liver as well as the bronchial glands, and the action of the liver in a common cold generally becomes somewhat defective.

One cannot leave the subject of benzoic acid without recalling Wöhler and Keller's well-known discovery, that when benzoic acid is introduced into the economy, it is eliminated by the kidneys entirely in the form of hippuric acid. The fact that the latter, when treated with boiling hydrochloric acid, splits up into benzoic acid and glycin, suggested that the hippuric acid consequent upon the ingestion of benzoic acid arises from the union of that substance with glycin. Seeing that the two bile-acids—glycocholic and taurocholic acids—are conjugates of cholalic acid with glycin and taurin respectively, the thought naturally arose that the formation of hippuric acid by the conjugation of benzoic acid with glycin probably takes place in the liver. This theory of the seat of its formation was supported by Kühne and Hallwachs (*Op.* xv.); but, on the other hand, Meissner and Shepard (*Op.* xvi.) maintained that the transformation of the benzoic acid takes place more in the kidneys than in the liver, and this opinion is supported by Schmiedeberg and Bunge (*Op.* xvii.). The evidence adduced by Kühne in favour of the liver as the exclusive seat of formation, or that by the other observers in favour of the kidney, need not here be entered into, for no light would thereby be thrown on the fact that, while benzoic acid is allying itself with glycin and carrying this substance into the urine, the hepatic cells are stimulated to produce more bile. In reviewing this subject, we have to express our regret that the bile was not analysed in the last two experiments, for the purpose of ascertaining whether or not its percentage amount of glycocholic acid was diminished, and to find out whether or not hippuric acid is excreted by the liver as well as by the kidney.*

*. Since the above was written we have ascertained that Mosler (*Op.* iii. p. 45) found, from several experiments on a dog with a permanent fistula, that when 60 and even 90 grains of benzoic acid are administered by the mouth, no hippuric acid is found in the bile. It is singular that he did not collect and measure the bile secreted daily, otherwise he would doubtless have anticipated our discovery of the stimulating effect of benzoic acid on the liver.

Action of Sodium Salicylate.

Scarcely anything is known regarding the physiological actions of salicylic acid. Bertagnini (quoted in *Op.* xviii. p. 696) took 100 grains within two days in 4-grain doses, and felt nothing but ringing in the ears and some degree of deafness. He observed that the acid was excreted in the urine in the form of salicyluric acid. It is known that this is a conjugate of salicylic acid and glycin. The formula of benzoic acid is $C_7H_6O_2$; that of salicylic acid, $C_7H_6O_3$. Their near chemical alliance and their similar behaviour towards glycin rendered it probable that salicylic acid, like benzoic acid, excites the hepatic cells. This substance has been lately much employed as a remedy in acute rheumatism. The dose for a man is from 15 to 20 grains.

Experiments 62, 66, and 67, already detailed, furnish abundant evidence of the remarkable powers of sodium salicylate as a stimulant of the liver, and other experiments yet to be described. Experiments 69, 70A, 73A, and 74A, furnish evidence still more striking; indeed, this substance is a certain hepatic stimulant, never failing, when placed in the duodenum, to excite the liver within half an hour. Owing to its certain and speedy action, it has been repeatedly used in the later experiments merely to furnish an effect which might be readily compared with that produced by some other substance. Table XXIV. gives the coefficients of bile-secretion under its influence.

Table XXIV.

Sodium Salicylate.	Total Dose in Grains.	Grains per kilogramme of Body-weight.	Secretion of Bile per kilogramme of Body-weight per hour.	
			Before.	After.
Experiment 74A, .	20	1.00	0.178 cc.	0.565 cc.
,, 62, .	25	1.55	2.260 cc.	0.664 cc.
,, 69, .	20	2.15	0.329 cc.	0.890 cc.

Result of Experiments with Sodium Salicylate.—It is a very powerful hepatic stimulant in the dog. Its slight action on the intestine is probably the reason why its effect on the human liver has passed unobserved by the physician. We have given to a man 30 grains of sodium salicylate at night, and next morning a purely intestinal stimulant, such as magnesium sulphate, and we feel convinced that there was an increased discharge of bile. We commend this point to the attention of physicians.

Action of Ammonium Phosphate and of Tannic Acid.

The similar effects produced on the liver by the sodium and ammonium salts of salicylic acid, led us to think again of the stimulating effect of sodium phosphate, and induced us to test the action of ammonium phosphate. It is employed in cases of chronic gout, and in urinary affections where uric acid calculi exist or threaten. Nothing has been hitherto known regarding its action on the liver, probably because it is not an intestinal stimulant; and, therefore, the increased secretion of bile—which it probably induces in man as it certainly does in the dog—has passed unobserved. The dose for a man is from 5 to 20 grains.

The first experiment with this substance yielded a negative result; but it has been thought right to discard it, because the ammonium phosphate was injected after liquor bismuthi into the same part of the intestinal canal.

Experiment 69. Dog that had fasted 17 hours. Weight 9.7 kilogrammes (Fig. 69).—20 grains of ammonium phosphate dissolved in 22 cc. of water, were injected into the duodenum at *a*. The subsequent increased bile-secretion was decided and prolonged. Since tannin is employed as an astringent in cases of diarrhœa, 20 grains, dissolved in 20 cc. of warm water, were injected into a fresh portion of the small intestine (*t*); but, as it did not affect the bile-secretion, it was not thought worth while to repeat the dose. 20 grains of sodium salicylate, in 10 cc. of water, were then injected into a fresh portion of the small intestine (*s*), and, within half an hour, its never-failing effect was evident. Obviously it stimulated the liver much more powerfully than ammonium phosphate. At the beginning

of the experiment, the coefficient of secretion was 0.19 cc. per kilogramme of body-weight per hour; a fair average for a fasting

Experiment 69.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.35		1.20	
0.50		1.05	
0.45	0.19 cc.	1.00	
0.40		0.90	
0.50		*t* ——	
a ——		0.90	
0.75		0.85	
0.80		0.80	0.329 cc.
1.10		0.80	
1.25		0.75	
1.10		*s* ——	
1.25		1.25	
1.30		2.50	0.89 cc.
1.50		2.65	
1.50		2.25	
1.55	0.634 cc.		
1.60			
1.50			

dog. After the ammonium phosphate, it rose to the unusually high figure of 0.634 cc.; but after the sodium salicylate, it rose still higher to 0.89 cc. The result of this experiment being apparently so unequivocal it was not thought necessary to repeat it. Nevertheless, considering the small size of the animal (9.7 kilos.), and that the dose was the maximum dose for a man, it seems reasonable to regard the effect of the ammonium phosphate in this case as perhaps unduly exaggerated.

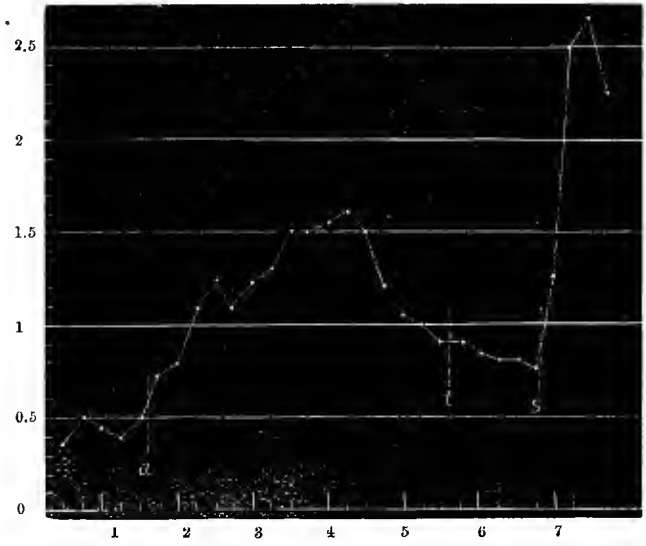
Necropsy.—Nothing notable observed in the intestine.

Result of Experiment with Ammonium Phosphate and Tannic Acid.—Ammonium phosphate is a powerful hepatic stimulant, but not so powerful as sodium salicylate. It is not an intestinal stimulant. Probably now that we have directed attention to the matter, it will be found to be a stimulant of the human liver also. Tannin does not appear to affect the liver.

Action of Acetate of Lead.

The well-known astringent effect of lead acetate in cases of diarrhœa renders it desirable to know whether or not it has the power of diminishing the secretion of bile. Röhrig (*Op.* vi. p. 270) experimented with acetate of lead, and found that 0.6 gramme (9.2 grains), dissolved in 4 ounces of warm water, and injected into the small intestine of a dog, diminished the secretion of bile. The erroneous nature of some of Röhrig's results, due to his very imperfect mode of experiment—as pointed out

Fig. 69.



Secretion of bile before and after ammonium phosphate, tannin, and sodium salicylate. 20 grains of ammonium phosphate in 22 cc. of water injected into the duodenum at *a*; 20 grains of tannin in 20 cc. of water injected at *t*; 20 grains of sodium salicylate in 10 cc. of water injected at *s*.

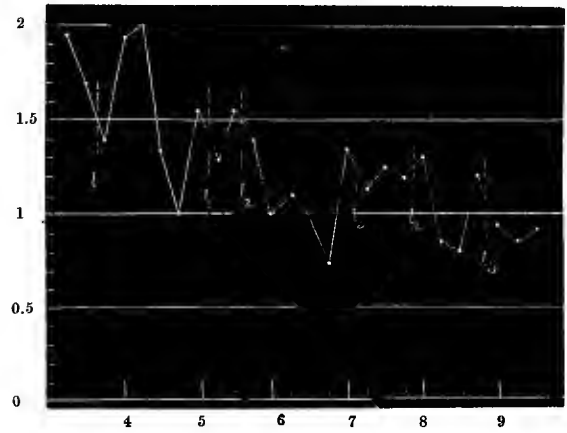
in the introduction—rendered necessary a re-investigation of the effects of lead acetate.

It has already been stated that, in Experiment 61A the administration of 8 grains of lead acetate was followed by a diminution of the bile-secretion, but that the result was of an equivocal nature. In Experiment 62 ten grains produced no

effect. In Experiment 64, a first dose of 8 grains, with a second dose of 12 grains, was indeed followed by a diminished bile-secretion; but, as stated in the description of that experiment, the result was entirely equivocal, and therefore other experiments were obviously required.

Experiment 70. Dog that had fasted 17 hours. Weight not ascertained (Fig. 70).—Owing to great difficulty in intro-

Fig. 70.



Secretion of bile before and after lead acetate. 2 grains in 15 cc. of water injected into the duodenum at l and l_1; 4 grains in 32 cc. of water at l_2; 4 grains in 15 cc. of water at l_3; 8 grains in 15 cc. of water at l_4; and 10 grains in 15 cc. of water at l_5 (30 grains given in all).

ducing the biliary cannula, and consequent serious disturbance of the bile-duct and its surroundings, the secretion of bile became, as mostly happens in such a case, very irregular; so much so, indeed, that the record of the first three hours is omitted from the chart. Two grains of lead acetate in 15 cc. of water were injected in the duodenum at l and l_1; 4 grains in 32 cc. of water at l_2; 4 grains in 15 cc. of water at l_3; 8 grains in 15 cc. of water at l_4; and 10 grains in 15 cc. of water at l_5. Thirty grains were given in all. The irregularity of secretion rendered the experiment unsatisfactory, and the discovery that the acetate of lead used in this and the previous experiments was impure, necessitated another experiment.

Experiment 70A. Dog that had fasted 18 hours. Weight 14.6 kilogrammes (Fig. 70A).—Ten grains of pure lead acetate,

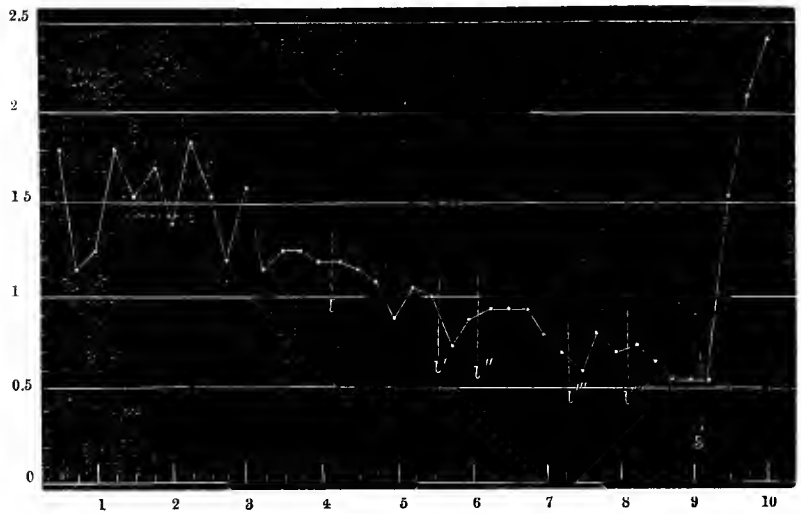
Experiment 70A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.8		0.75	
1.15		0.90	
1.25		*l″* ——	
1.80		0.95	
1.55		0.95	
1.70		0.95	
1.40		0.80	
1.85		0.70	
1.55		*l‴* ——	
1.20		0.60	
1.60		0.80	
1.15		0.70	
1.25	0.331 cc.	*l⁗* ——	
1.25		0.75	0.171 cc.
1.2		0.65	
l ——		0.55	
1.2		0.55	
1.15		*s* ——	
1.10		0.55	
0.90		1.55	0.452 cc.
1.05		2.10	
1.00		2.40	
l′ ——			

dissolved in 10 cc. of distilled water, were injected into the duodenum at *l*, *l′*, *l″*, *l‴*, and *l⁗*; 50 grains in all being given. The decided fall in secretion towards the close of this experiment is abnormal, and may fairly be ascribed to a depressant effect of the lead; but it is obvious that the first doses did not produce the effect which might have been anticipated from Röhrig's experiments. That the liver was not exhausted, however, and was capable of increased action, was proved by injecting into the duodenum 20 grains of sodium salicylate dissolved in 10 cc. of water. Although it was the ninth hour of the experiment, the biliary secretion became greatly accelerated, and reached a point decidedly higher than it had been at the beginning of the experiment. All the more, therefore, may the previously diminished secretion be ascribed to the depressant action of the lead; while it is obvious that an

ordinary dose of sodium salicylate can excite the liver thus poisoned and depressed.

Fig. 70A.



Secretion of bile before and after lead acetate and sodium salicylate. 10 grains of lead acetate in 20 cc. of water injected into the duodenum at *l* and *l'*; 10 grains in 10 cc. of water at *l''*, *l'''*, and *l''''*; 20 grains of sodium salicyate in 10 cc. of water injected into the duodenum at *s*.

Result of Experiments with Lead Acetate—In large doses, it has a depressant effect on the secretion of bile. Sodium salicylate can overcome that effect. The obstinate constipation observed in cases of lead-poisoning may, to some extent, be owing to the depressant effect of lead on the liver; but it is probably chiefly owing to a depressant action on the intestinal glands; for, in view of the astringent effect of a dose of from 1 to 4 grains in diarrhœa, it seems likely, from the above experiments, that it affects the intestinal canal more than the liver. It is a remarkable fact that, of all the substances employed in this research, lead acetate is the only one which depresses the action of the liver without producing purgation. It seems to be a direct hepatic depressant. As previously explained, every purely intestinal purgative agent depresses hepatic action, in a manner which is probably, however, purely indirect, and to which allusion will again be made in the sequel.

Action of Jaborandi.

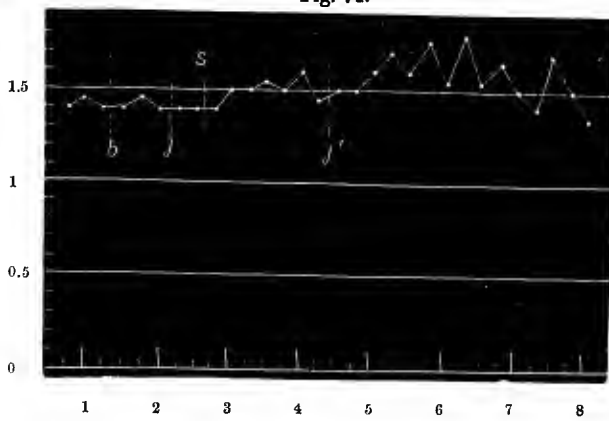
Jaborandi being a powerful stimulant of the salivary and sweat glands, we thought it desirable to ascertain its influence on the liver. The mean dose for a man is a watery infusion of sixty-four grains of the leaves.

Experiment 71.		Experiment 71A.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.40		1.80	
1.42		1.70	
1.40		1.67	
b——		1.70	
1.40		*b*——	
1.45	0.265 cc.	1.70	
1.40		1.72	0.314 cc.
j——		1.65	
1.40		1.70	
1.40		*j*——	
s——		1.70	
1.40		1.60	
1.50		*s*——	
1.50		1.60	
1.55		1.70	
1.50		1.60	
1.60		1.75	
1.45		1.80	
j′——		1.75	
1.50		1.90	
1.50		1.95	
1.60		2.00	
1.70		1.80	0.365 cc.
1.60	0.310 cc.	2.00	
1.72		2.05	
1.55		1.85	
1.80		1.72	
1.55		1.60	
1.65		*j′*——	
1.50		1.50	
1.40		1.52	
1.70		1.62	
1.50		1.67	
1.35		1.70	
		1.75	

Experiment 71. Dog that had fasted 18 hours. Weight 21.5 kilogrammes (Fig. 71).—Eight cc. of water with 2 cc. of bile

were injected into the duodenum at *b*, and 8 cc. of a concentrated aqueous infusion containing the active principle of 64 grains of

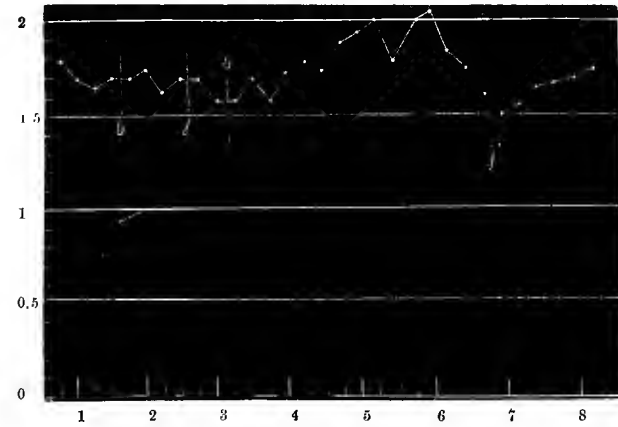
Fig. 71.



Secretion of bile before and after jaborandi. 2 cc. of bile and 8 cc. of water injected into the duodenum at *b*; 8 cc. of infusion of jaborandi with 2 cc. of bile injected at *j* and *j'*; salivation began at *s*.

jaborandi leaves were injected at *j*, and the same dose was again given at *j'*. Powerful salivation began half an hour after the first dose (at *s*), and it is to be observed that shortly afterwards

Fig. 71A.



Secretion of bile before and after jaborandi. At *b*, 2 cc. of bile and 10 cc. of water; at *j* and *j'* the same fluid, with 10 cc. infusion of 75 grains of jaborandi leaves, injected into the duodenum. Salivation began at *s*.

the bile-secretion also underwent a slight increase, that became more marked after the second dose.

NECROPSY.—Ninety-seven cc. of liquid in the small intestine (30 cc. had been injected), but whether most of it had been secreted by the pancreas or by Lieberkühn's follicles was undetermined. There was no unusual redness of the intestinal mucous membrane.

Experiment 71A. Dog that had fasted 18 hours. Weight 21.5 kilogrammes (Fig. 71A).—Ten cc. of water with 2 cc. of bile were injected into the duodenum at *b*, and the same fluid, with 10 cc. of aqueous infusion of jaborandi, was injected at *j* and again at *j'*. As each cubic centimeter of the infusion contained the active principle of 7½ grains of the leaves, 150 grains had been given. Salivation began half an hour after the first dose, and soon thereafter the bile-secretion rose, but to no great extent. It was observed in this experiment that the *bronchial glands were much stimulated* by the jaborandi, the respiratory cannula being completely obstructed by a watery mucus, which must have been secreted in the bronchi and trachea.

NECROPSY.—The jaborandi had traversed the whole length of the small intestine, which contained 107 cc. of a clear greenish fluid without mucous flakes. Thirty-six cc. of fluid had been injected; but how much of the remainder had been secreted by the pancreas and how much by Lieberkühn's follicles could not be determined.

Result of Experiments with Jaborandi.—In doses that were much more than sufficient to excite the salivary glands, jaborandi produced only a slight increase in the biliary secretion. It is therefore to be regarded as a very feeble hepatic stimulant.

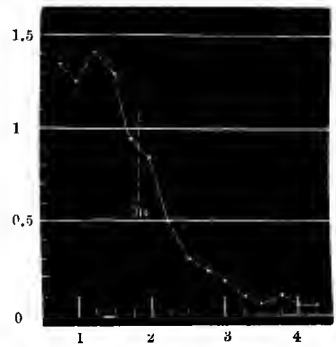
ACTION OF SULPHATE OF MANGANESE.

It is stated by Pareira (*Op.* xix. I. p. 635) that "C. G. Gmelin tried the effect of the sulphate of the protoxide of manganese on animals, and found that it caused vomiting, paralysis with convulsions, and inflammation of the stomach, small intestines, liver, spleen, and heart. He notices as a remarkable fact, the extraordinary secretion of bile produced by it, and which was

so considerable that nearly all the intestines were coloured by it, and the large intestines had a wax-yellow colour communicated to them." At the suggestion of Pareira (*loc. cit.*), its effects on the human subject were tested by Mr Ure, who found that, in doses of from 60 to 120 grains, it acts as a purgative and cholagogue. In a recent communication to the *Lancet* (1878, i. 882), Dr R. H. Goolden states that he has been in the habit of using the substance as a cholagogue for more than thirty years. He finds that, in doses of from ten to twenty grains, it produces large bilious evacuations. Ten grains he regards as a sufficient dose for ordinary purposes. This he dissolves in a tumbler of water, and adds some citrate of potash or magnesia. These statements rendered it desirable for us to test the action of this substance by our method of experiment.

Experiment 72. Dog that had fasted 18 hours. Weight 15 kilogrammes (Fig. 72).—Thinking, from Pareira's statement of

Fig. 72.



Secretion of bile before and after sulphate of manganese. 60 grains of manganese sulphate in 30 cc. of water injected into the duodenum at *m*.

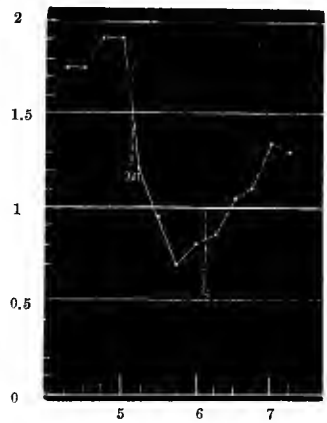
the amount given to the human subject by Ure, that 60 grains of manganese sulphate would not be too large a dose for a dog, we injected that amount in 30 cc. of water into the duodenum at *m*. So far from any increase of the bile-secretion resulting, there was a decided fall, the secretion coming nearly to a standstill. The weak pulse of the animal suggested that collapse had been occasioned by the drug, and the necropsy fully confirmed the idea that too much had been given. The fall of secretion,

however, was in the first instance indirectly due to the effects of the powerful purgation that was induced, though the very low secretion at the close was, in all probability, due to collapse.

NECROPSY.—Evidence of powerful purgation in the upper third of small intestine. Very violent irritation of the mucous membrane of this region of the gut, the surface of which was covered with a yellowish-white pulpy matter, as if the epithelium had been dissolved by a caustic alkali.

Experiment 72A. Dog that had fasted 18 hours. Weight 17.7 kilogrammes (Fig. 72A).—As the dose in the previous

Fig. 72A.



Secretion of bile before and after manganese sulphate and sodium benzoate. 20 grains of manganese sulphate in 15 cc. of water injected into the duodenum at *m*; 21 grains of sodium benzoate in 15 cc. of water injected at *s*.

case had evidently been too large, only 20 grains of manganese sulphate were given, in the same manner as before, in this instance (*m*). But there was not the slightest rise in the bile-secretion; on the contrary, there was a decided fall, as is the rule under the influence of a substance that produces purgation without exciting the liver. It now came to be the question, Would the bile-secretion rise in spite of the purgative drain from the portal vein, if a hepatic stimulant were administered? To determine this, 21 grains of sodium benzoate in 15 cc. of water were injected into the duodenum at *s*; and, in spite of the disadvantageous circumstance of its being introduced into a

column of intestinal juice actively being secreted, it excited the liver to secrete more bile, showing that the liver could be excited by a substance possessed of the property of so doing.

NECROPSY.—Copious watery purgation throughout the whole length of small intestine, whose mucous membrane was, however, scarcely at all reddened. The dose had, therefore, been efficient as an intestinal, but not as a hepatic, stimulant.

Results of Experiments with Manganese Sulphate.—Experiments 72 and 72A entirely bear out the statement that manganese sulphate is an intestinal stimulant, but lend no support to the idea that it is a hepatic stimulant. The effect on the biliary secretion is, indeed, similar to that of magnesium sulphate (p. 69), or any other purely intestinal stimulant; that is, it diminishes the biliary secretion, probably by draining the portal system. Yet Dr Goolden's statements are explicitly to the effect (*lib. cit.*) that the same result was not produced by sulphate of magnesia as by sulphate of manganese. We cannot, of course, from the above experiments, deny that the manganese salt is a cholagogue in man; but, looking to the general harmony between our observations on the dog and those on man, we think we are entitled to throw very grave doubts upon the idea that manganese sulphate excites the human liver. It might, indeed, be maintained that it has the power of inducing contractions of the gall-bladder and larger bile-ducts, and of thus increasing the amount of bile in the dejections; but we can only commend to the attention of physicians Dr Goolden's positive observations as to the increased amount of bile in the dejections of man, and our negative results as to any stimulating effect on the bile-secreting mechanism of the dog.

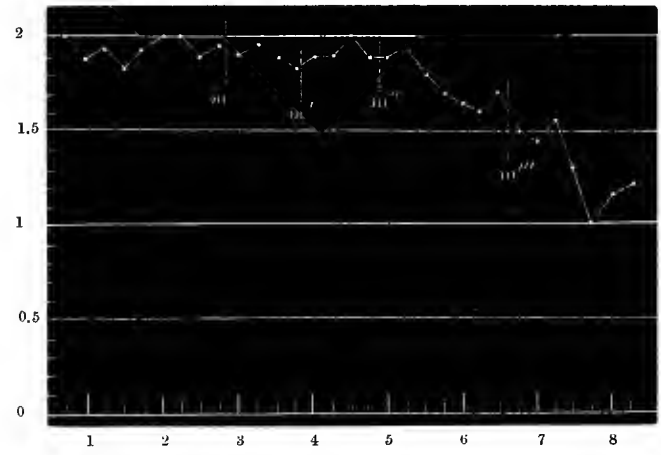
ACTION OF MORPHIA.

As morphia has the well-known power of arresting diarrhœa and of producing constipation, it is desirable to know whether this is to be ascribed to its effect on the intestine alone, or also to a power of diminishing the secretion of bile.

Experiment 73. Dog that had fasted 18 hours. Weight 33 kilogrammes (Fig. 73).—One grain of morphia hydrochlorate

in 3 cc. of bile and water was injected into the duodenum at *m*, *m'*, *m''*, and *m'''*, 4 grains being given in all. The first two

Fig. 73.



Secretion of bile before and after morphia hydrochlorate. 1 grain with 2 cc. of bile and 1 cc. of water injected into the duodenum at *m*, *m'*, *m''*, and *m'''*.

doses had no obvious effect on the bile-secretion; but it began to fall after the third, and continued to do so after the fourth, doses. As it was impossible to know, from this single experiment, whether or not this fall in the secretion was due to the morphia, a second experiment was performed.

NECROPSY.—The mucous membrane of the small intestine was almost dry.

Experiment 73A. Dog that had fasted 18 hours. Weight 19.9 kilogrammes (Fig. 73A).—One grain of acetate of morphia in 5 cc. of water was injected into the duodenum at *m*, and 2 grains in 10 cc. of water were injected at *m'*. The morphia did not appear to affect the secretion. As it seemed desirable to know whether or not the liver of an animal so narcotised could be excited by an appropriate stimulant, 20 grains of sodium salicylate in 10 cc. of water were injected into the duodenum at *s*. Powerful and prolonged excitement of the liver was the result.

NECROPSY.—Slightly increased redness of the duodenal mucous

membrane. Evidence of slight purgative action in the upper part of the small intestine.

Experiment 73A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.15		*s* ——	
0.85		1.05	
0.80		3.05	
0.70	} 0.15 cc.	3.35	} 0.565 cc.
0.70		2.45	
0.80		2.40	
m ——		2.15	
0.95		2.30	
1.10		2.30	
0.95		2.30	
m′ ——		2.60	
0.90		2.60	
0.85	}		
0.75			
1.05	} 0.178 cc.		
0.90			

Results of Experiments with Morphia.—Three grains of morphia acetate did not affect the secretion of bile.

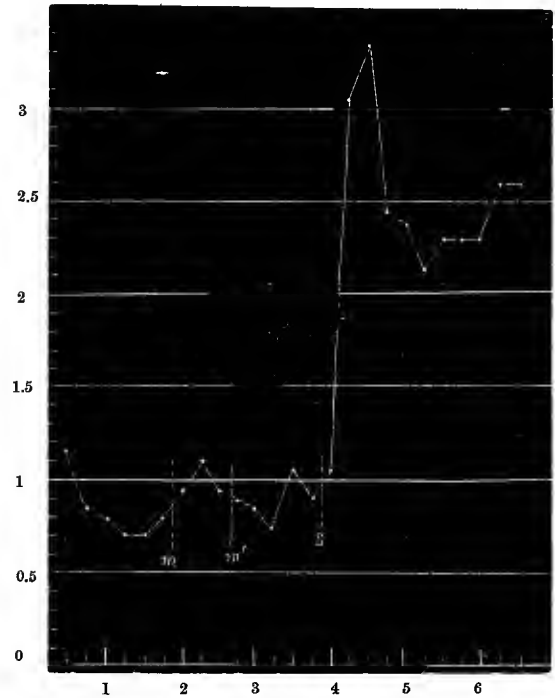
Action of Hyoscyamus.

As extract of hyoscyamus is often administered with cholagogue substances, it is important to know whether or not it diminishes the secretion of bile. The dose of this substance for a man is from 5 to 10 grains.

Experiment 74. Dog that had fasted 18 hours. Weight 21 kilogrammes (Fig. 74).—Two grains of aqueous extract of hyoscyamus in 3 cc. of water were injected into the duodenum at *h*, *h′*, *h″*, and *h‴*, 8 grains being given in all. It was impossible, from this single experiment, to say whether or not the fall in the secretion was due to the hyoscyamus; but the unusually high coefficient of secretion in the earlier part of the experiment (0.311 cc. per kilogramme per hour) favoured the conclusion that the fall was not due to the drug.

NECROPSY.—Mucous membrane of small intestine pale and dry.

Fig. 73A.



Secretion of bile before and after morphia and sodium salicylate. 1 grain of morphia acetate in 5 cc. of water injected into the duodenum at *m*; 2 grains in 10 cc. of water at *m'*; 20 grains of sodium salicylate in 10 cc. of water injected into the duodenum at *s*.

Experiment 74A. Dog that had fasted 18 hours. Weight 16.8 kilogrammes (Fig. 74A).—To decide the point left in doubt by the previous experiment, larger doses of the drug were administered. Eight grains of the extract of hyoscyamus triturated with 1 cc. of bile and 10 cc. of water were injected into the duodenum at *h*, and the same dose was injected into a lower part of the intestine at *h'*. It is difficult to account for the slight rise of secretion that followed both doses. It may be safely assumed that it was due neither to the bile nor to the water. At all events, there was no fall of secretion, notwithstanding the administration of sixteen grains of the drug.

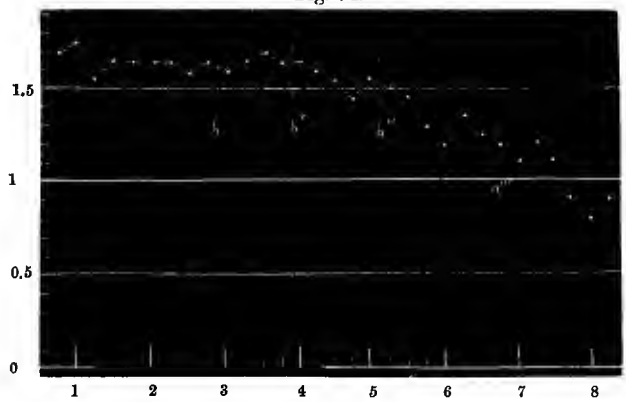
As the experiment was entirely conclusive regarding the effect of hyoscyamus, it was proposed to investigate the action

Experiment 74.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.7		1.45	
1.75		1.55	
1.55		h'' ——	
1.65		1.50	
1.65		1.45	
1.65		1.30	
1.65	0.311 cc.	1.20	
1.60		1.35	
1.65		1.25	
h ——		h''' ——	
1.60		1.20	
1.65		1.10	
1.70		0.90	
1.65		0.80	
h' ——		0.90	0.176 cc.
1.65		0.80	
1.60		0.90	
1.55			

of pure alcohol; accordingly 5 cc. of absolute alcohol, diluted with 32 cc. of water, were injected into a fresh portion of the

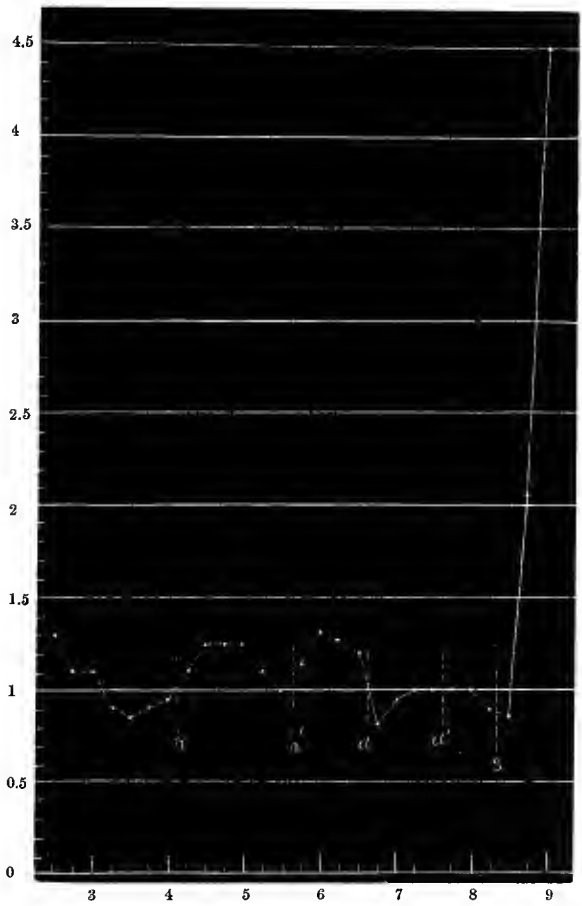
Fig. 74.



Secretion of bile before and after hyoscyamus. 2 grains of extract of hyoscyamus with 3 cc. of water injected into the duodenum at h, h', h'', and h'''.

small intestine, and, as there was no notable effect, 8 cc. of absolute alcohol in 32 cc. of water were injected into another

Fig. 74A.



Secretion of bile before and after hyoscyamus and absolute alcohol. 8 grains of extract of hyoscyamus in 10 cc. of water and 1 cc. of bile injected into the duodenum at *h*; the same, injected into a lower part of the small intestine, at *h'*; 5 cc. of absolute alcohol in 20 cc. of water injected into the small intestine at *a*; 8 cc. of absolute alcohol in 32 cc. of water injected into the small intestine at *a'*; 20 grains of sodium salicylate in 10 cc. of water injected into the duodenum at *s*.

part of the gut. Notwithstanding the administration of 13 cc. of alcohol (219 minims), the bile-secretion was virtually unaf-

fected. It was now sought to determine what such a liver could do if stimulated. Twenty grains of sodium salicylate in

Experiment 74A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.30		1.30	
1.10		1.25	
1.10		1.20	
0.90		*a*——	
0.85	0.214 cc.	0.80	
0.90		0.95	
0.95		1.00	
h——		1.00	0.231 cc.
1.10		*a′*——	
1.25		1.00	
1.25	0.288 cc.	1.00	
1.25		0.90	
1.10		*s*——	
1.00		0.85	
h′——		2.05	
1.15		4.50	

10 cc. of water were injected into the duodenum at *s*, and speedily thereafter the bile-secretion was enormously increased, and that so late as the ninth hour of the experiment.

Result of Experiments with Hyoscyamus.—Sixteen grains of extract of hyoscyamus, prepared according to the *British Pharmacopœia*, did not notably affect the biliary secretion, and did not prevent such a stimulant as sodium salicylate from augmenting it. From observations on the human subject, we are also able to state that hyoscyamus does not seem to interfere with the stimulating effect of euonymin on the liver, and very probably it may be safely given with all hepatic stimulants that are also intestinal stimulants, and happen to cause griping.

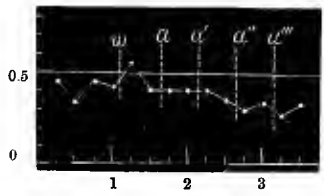
Action of Alcohol.

It is a matter of common opinion that alcoholic drinks affect the action of the liver; but, whether their hepatic effects may be ascribed to the alcohol, ethers, or other substances they contain,

no one has hitherto sought to determine. The results of the preceding experiment already go far to determine the question as regards pure alcohol; but as hyoscyamus had in that experiment been previously administered, it was desirable to perform another experiment in which nothing but pure, diluted alcohol should be administered.

Experiment 74B. A small dog (not weighed) that had fasted 18 hours (Fig 74B).—Fifteen cc. of water were injected

Fig. 74B.



Secretion of bile before and after alcohol. At *w* 15 cc. of water; at *a*, *a'*, *a''*, *a'''*, 5 cc. of absolute alcohol with 15 cc. of water injected into the stomach through an œsophagus tube.

into the stomach through an œsophagus tube (*w*); then 5 cc. of absolute alcohol diluted with 15 cc. of water were injected into the stomach in the same manner at *a*, *a'*, *a''*, *a'''*, 20 cc. (338 minims) being given in all.

Result of Experiments with Alcohol.—In Experiment 74A, 13 cc. of absolute alcohol, and in Experiment 74B, 30 cc. of absolute alcohol, moderately diluted and introduced into the alimentary canal, did not produce any apparent effect on the biliary secretion. These experiments, however, furnish no evidence of what might be the effects of the prolonged action of alcohol on the liver; and, in consideration of the great labour and length of this research, we could not undertake experiments designed to show the effects of various sorts of alcoholic drinks, or of the substances other than alcohol which they contain. Such research could scarcely be of great practical importance, for we already know that certain alcoholic drinks—such as ale, stout, &c.—tend to produce "biliousness;" and, by experiments on the human subject, we have ascertained that the condition, thus induced, may be cured by giving iridin or euonymin, substances which powerfully stimulate the liver. As far as they go, how-

ever, our experiments show that *pure alcohol* has, at all events, *no immediate* action on the liver of the dog.

Action of Mercurial Salts.

Calomel, and mercury in the form of blue pill, are the two preparations of mercury commonly employed for the purpose of inducing purgative action. The most generally received opinion regarding the action of calomel as a cholagogue is thus expressed by Christison (*Op.* xii. p. 505):—"The cathartic action of calomel and other mercurials is uncertain, unless other cathartics are united with them. Their action on the bowels is believed to be always attended by an increased discharge of bile from the gall-bladder." But, although this has long been the prevalent opinion, some physicians have doubted the cholagogue property of calomel, and on that account several attempts have been made to determine its action by experiments on animals. Nasse (*Op.* i. p. 158) seems to have been the first to make the attempt. He established a permanent biliary fistula in the manner already indicated (p. x), and he found that calomel increased the absolute quantity of fluid bile, but diminished its solid constituents. By a similar method Kölliker and Müller (*Op.* ii.) found that 4 grains of calomel given to a dog diminished the secretion of bile. Mosler (*Op.* iii.), adopting also the method of permanent fistula, found, that even when large doses of calomel were administered, not a trace of mercury was found in the bile. Scott (*Op.* iv.) gave to a dog with a permanent biliary fistula 3 grains, 6 grains, and 12 grains of calomel on separate occasions. He collected the bile continuously before, during, and after each dose of the mercurial, and he found but one result, viz., a diminution in the amount of bile and bile-solids secreted after the administration of these doses. Scott's experiment appears to have been very carefully conducted. Its result was so much at variance with the prevalent opinion regarding the action of calomel in man, that some authorities alleged that there must be some difference between the action of mercurials on man and on the dog. Impressed with

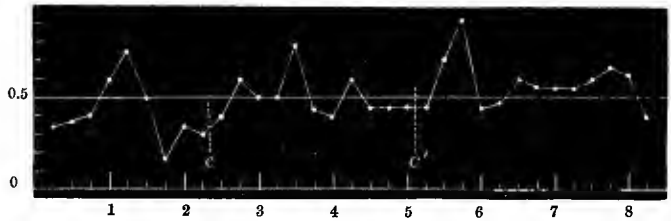
the necessity for obtaining precise information with regard to this point and others, Hughes Bennett organised the committee to which reference has already been made. The committee settled beyond all possibility of doubt that mercury produces in the dog the same general effects as in man (*Op.* v. p. 201). When small but increasing doses of corrosive sublimate were injected under the skin for several days in succession, salivation occurred, the breath became fœtid, the gums ulcerated, emaciation ensued, and in dogs without biliary fistulæ (when therefore the bile was discharged into the intestine) the drug set up profuse diarrhœa, while in dogs with biliary fistulæ there was no diarrhœa. The significance of this fact struck no one at the time, but the experiments hereafter to be detailed (p. 149) suggest that the diarrhœa was probably bilious. The committee further found (*Op.* v. p. 214) that when calomel was administered to dogs with permanent biliary fistulæ in doses of one-twelfth of a grain given from six to fourteen times daily, and in doses of 2 grains from two to six times daily, it did not increase the biliary secretion, nor did it produce purgation; but when given in doses of 10 grains once a day, it produced purgation and diminished the biliary secretion. More recently experiments were performed by Röhrig (*Op.* vi. p. 254), who found by the method of temporary fistula, that when "calomel was administered to dogs in large doses (20 grains), it rarely happened that the secretion of bile was recalled after it had come to a standstill, although it increased the secretion when it was only diminishing." The imperfections of Röhrig's method render such a statement of very little value. Our method of experiment being better adapted to afford accurate data, we performed the following experiments:—

Experiment 75. Dog that had fasted 18 hours. Weight 19.6 kilogrammes (Fig. 75).—10 grains of calomel in 7 cc. water were injected into the duodenum at *c*, and the same dose was repeated at *c'*.

Necropsy.—There was evidence of a profuse purgative effect, the small intestine containing a large quantity of a thick greyish fluid with greenish flakes. The mucous membrane was pale throughout the greater part of its extent, but at intervals in the duodenum there were limited areas of redness. The post-

mortem examination in this case was not made until fourteen hours after death.

Fig. 75.



Secretion of bile before and after calomel given without bile. 10 grains calomel in 7 cc. water injected into duodenum at *c*, and again at *c'*.

In Experiment 75 the administration of 20 grains of calomel in two doses of 10 grains was followed by a powerful purgative effect and by a slight increase in the bile-secretion; but, consider-

Experiment 75.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
0.30		0.45	
0.32		0.45	
0.35	0.103 cc.	0.45	0.091 cc.
0.60		*c'* ——	
0.76		0.45	
0.50		0.72	
0.17	0.067 cc.	0.97	0.133 cc.
0.35		0.45	
0.30		0.47	
c ——		0.60	
0.40		0.57	0.116 cc.
0.60	0.102 cc.	0.55	
0.50		0.57	
0.50		0.60	
0.80		0.72	0.12 cc.
0.45	0.114 cc.	0.65	
0.40		0.40	
0.60			

ing that the coefficient of secretion never rose above 0.133 cc., it is evident that the increased activity of the liver was very trifling. Yet one would be apt to be misled by such an experiment as this, had we, after the manner of Röhrig, failed to show

the amount of bile secreted in relation to the weight of the animal. Judging from subsequent experiments, it can scarcely be doubted that the trifling increase of secretion in this experiment had nothing to do with the calomel.

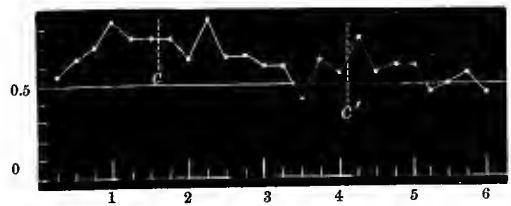
Experiment 75A. Dog that had fasted 18 hours. Weight 7 kilogrammes (Fig. 75A).—10 grains of calomel in 3 cc. water

Experiment 75A.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
0.57		0.60	
0.65		0.40	0.31 cc.
0.70		0.65	
0.85	0.43 cc.	0.57	
0.75		*c′* ——	
0.75		0.75	
c ——		0.52	
0.75		0.60	0.36 cc.
0.65		0.60	
0.87		0.45	
0.62		0.50	0.27 cc.
0.67		0.55	
0.60		0.45	

were injected into the duodenum at *c*, and again at *c′* (20 grains given in all).

Fig. 75A.



Secretion of bile before and after calomel given without bile. 10 grains calomel in 3 cc. water injected into duodenum at *c*, and the same dose repeated at *c′*.

NECROPSY.—The upper third of the small intestine was semi-distended with a brown, somewhat clear, viscous fluid, with patches of green, thus affording evidence of purgative action. The gastric mucous membrane was pale, and contained some viscous fluid of a brownish colour, with a patch of green matter

clinging to the mucous membrane near to the pylorus, which was evidently due to the entrance of calomel from the duodenum, for a little unchanged calomel was perceptible at the margin of the patch. The cause of the brown colour of the fluid was not apparent. The necropsy was in this case performed fifteen hours after death.

The exceptionally high secretion in Experiment 75A was probably due to the circumstance that the animal was a young one. In proportion to the weight of the animal, more bile is secreted by a young than by a full-grown dog. The administration of calomel was followed by decided purgation and by diminished bile-secretion.

Experiment 75B. Dog that had fasted 18 hours. Weight

Experiment 75B.

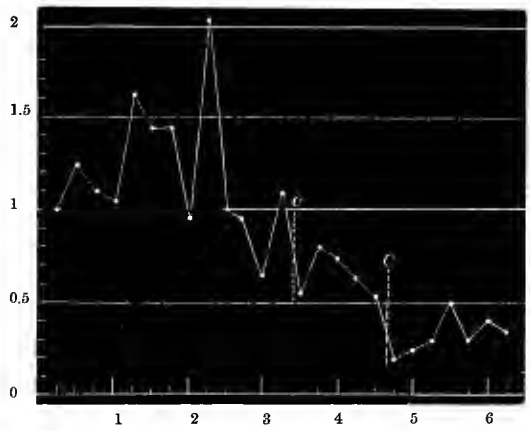
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.00		c ——	
1.25		0.56	
1.12		0.80	
1.07		0.74	0.29 cc.
1.65		0.62	
1.45		0.54	
1.42		c' ——	
0.97		0.20	
2.05		0.28	
1.00		0.32	
0.94	0.28 cc.	0.50	
0.62		0.30	0.12 cc.
1.12		0.40	
		0.36	

12.9 kilogrammes (Fig 75B).—The secretion of bile was unfortunately very irregular in the early part of the experiment. Ten grains of calomel in 9 cc. water were injected into the duodenum at c, and again at c'; 20 grains being given in all. A profuse purgative action was the result, but the bile-secretion was only lowered.

NECROPSY.—Stomach contained a colourless mucous fluid, with here and there a green patch of calomel that had entered it through the pylorus. The upper half of the small intestine contained a large quantity of a greyish fluid with green patches,

thus affording evidence of powerful purgative effect. The mucous membrane in this region of the intestine was very vascular.

Fig. 75B.



Secretion of bile before and after calomel given without bile. 10 grains calomel in 9 cc. water injected into duodenum at *c*, and the same dose repeated at *c'*.

The general result of the three preceding experiments is that calomel did not stimulate the liver, although it did not fail to stimulate the intestinal glands. But it is to be observed that the calomel was introduced into the duodenum suspended in water, it could not come into contact with bile in the intestine, for, owing to the fasting condition of the animal previous to the establishment of the fistula, there was no bile there. Calomel is insoluble in water, and as Headland (*Op.* xx. p. 380) had pointed out that it is to a slight exteut soluble in bile, we were led to suppose that possibly its non-action on the liver in these cases might have resulted from the absence of bile from the intestinal canal. And it was apparent that this source of fallacy had also vitiated every experiment that had been performed by previous observers. We accordingly performed the two following experiments, in which the calomel was mixed with bile, and then injected into the duodenum, and we gave smaller doses than in the preceding experiments.

Experiment 76. Dog that had fasted 17 hours. Weight 14.7 kilogrammes (Fig. 76).—2.5 cc. water and 0.5 cc. bile

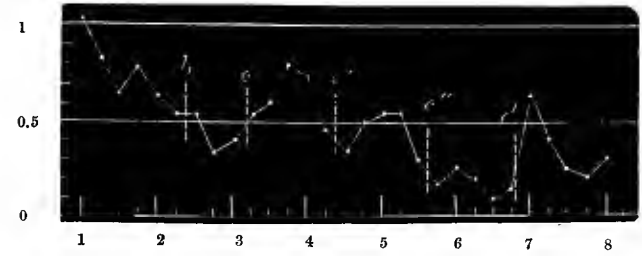
were injected into the duodenum at *b*, and 2 grains of calomel in the same fluid at *c*, *c'*, *c''*, and *d*, 8 grains being given in all. Unfortunately, the secretion of bile was very irregular. The main result of the experiment was diminished biliary secretion, still the slight increments of secretion that followed the first, second, and fourth doses, rendered a repetition of the experiment desirable.

Experiment 76.		Experiment 76A.	
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.05		1.80	
0.85		1.90	
0.65		1.80	
0.80		1.70	
0.65		1.70	
0.55		1.65	
b ——		*b* ——	
0.55	0.125 cc.	1.65	0.258 cc.
0.35		1.70	
0.40		1.65	
c ——		*c* ——	
0·55		1.70	
0.60	0.196 cc.	1.70	
0.80		1.65	
0.75		1.62	
0.45		*c'* ——	
c' ——		1.60	
0.35		1.62	0.248 cc.
0.50		1.57	
0.55	0.129 cc.	1.62	
0.55		*c''* ——	
0.30		1.62	
c'' ——		1.60	
0.15		1.55	
0.25		1.60	
0.20		*c'''* ——	
0.10		1.50	
0.15		1.40	
d ——		1.50	
0.65		1.40	
0.40	0.108 cc.	*c*⁴ ——	
0.25		1.40	
0.20		1.30	
0.30		1.40	0.204 cc.
		1.30	
		1.25	

NECROPSY.—The upper half of the small intestine contained evidence of decided purgation. Its mucous membrane was considerably congested.

Experiment 76A. Dog that had fasted 17 hours. Weight 25.7 kilogrammes (Fig. 76A).—2.5 cc. water and 0.5 cc.

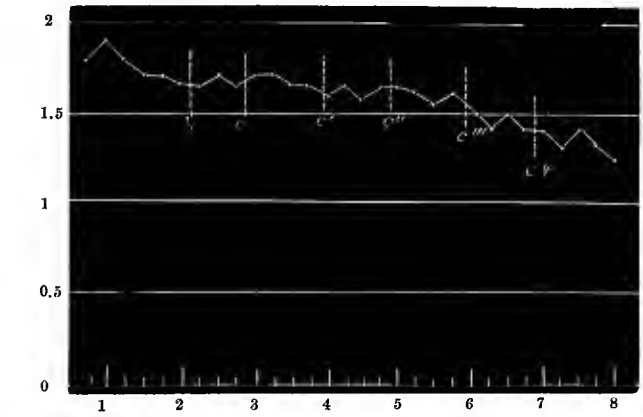
Fig. 76.



Secretion of bile before and after calomel given with bile. 0.5 cc. bile and 2.5 cc. water injected into duodenum at *b*. 2 grains calomel in the above fluid injected into duodenum at *c*, *c'*, *c''*, and *d*, respectively.

bile were injected into the duodenum at *b*, and 1 grain of calomel in the same fluid was injected at *c*, *c'*, *c''*, *c'''* and c^4: 5 grains being given in all. The bile-secretion was never increased.

Fig. 76A.



Secretion of bile before and after calomel given with bile. 0.5 cc. bile and 2.5 cc. water injected into duodenum at *b*. 1 grain calomel in the above fluid injected into duodenum at *c*, *c'*, *c''*, *c'''*, c^4, respectively.

NECROPSY.—The upper half of the small intestine contained 187 cc. of a viscous fluid with grey flakes; thus affording evidence of strong purgation. The vascularity of the mucous membrane was decidedly increased.

Result of Experiments with Calomel mixed with Bile.—The biliary secretion in Experiment 76A was so regular, and the doses of calomel so graduated, that its result may be regarded as conclusively showing that calomel, when mixed with bile and placed in the duodenum, does not excite the liver, although it powerfully stimulates the intestinal glands. *The addition of bile to the calomel made therefore no difference in the result.*

As is well known, Miahle (*Chimie Appliquée*) ascribed all the effects of calomel, and other mercurial preparations, to the production of mercuric chloride, by the action of the alkaline chlorides in the secretions of the alimentary canal, more especially in the gastric juice. This theory has, however, been strongly opposed by Buchheim, Œtinger, and Winckler (referred to by Wood in *Op.* xi. p. 330), on the grounds that, at a temperature so low as that of the body, calomel undergoes no transformation into mercuric chloride in a solution of alkaline chlorides. Nevertheless, one must remember that the gastric juice contains free hydrochloric acid. The amount is only 0.02 per cent. in the juice of man, mixed with saliva; in that of the dog, the amount is 0.031 per cent. (C. Schmidt). When Miahle wrote, the free acid of the gastric juice was thought to be lactic; therefore the effect of very dilute hydrochloric acid on calomel, at the body temperature, has not hitherto been investigated. As no conclusion could be legitimate in the absence of definite information on this point, we performed the following experiment:—

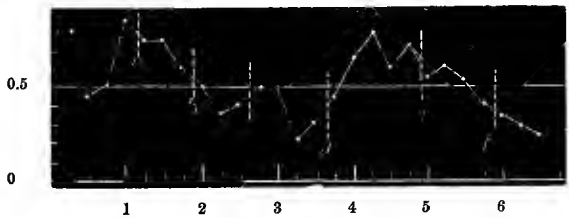
Experiment 77.—Calomel was washed with ether, the filtrate tested with caustic potash, and proved to contain no mercuric chloride. Of the calomel—thus ascertained to be pure—we placed three grammes in 500 cc. distilled water containing 0.02 per cent. anhydrous hydrochloric acid, and submitted the whole to a constant temperature of 100° Fahr.—the temperature of the stomach—for thirty-six hours. The fluid was then filtered, concentrated, and tested with sulphuretted hydrogen. A distinct precipitate—first white, then changing to yellow, and finally to black—was obtained, thus proving the presence of corrosive sublimate. Judging from the precipitate, the amount was considerable; but a large quantity of calomel had been employed, and it had been acted on by the acid for a lengthened period.

We repeated the experiment, using the same amount of calomel and acid fluid, but keeping it only seventeen hours at the temperature of the body. The fluid was then filtered, the filtrate evaporated, the residue dried and weighed, and it was found that three grammes of calomel had yielded 17 milligrammes of mercuric chloride. Under similar circumstances, 5 grains of calomel—the ordinary dose for a man—would, if digested seventeen hours with about 50 cc. acid fluid, have yielded $\frac{1}{35}$ grain mercuric chloride. Whether or not so minute a quantity of the latter substance is likely to affect the human liver will be considered in the sequel. Calomel is usually taken at bed-time on an empty stomach. We do not know if it can call forth a secretion of gastric juice sufficient to exert an appreciable influence upon it; but in any case, it probably does not remain in the stomach more than five or six hours at the utmost. We however postpone for the present the further consideration of this point.

Obviously, our next duty was to ascertain whether or not corrosive sublimate has the power of stimulating the liver.

Experiment 78. Dog that had fasted 17 hours. Weight 8.8 kilogrammes (Fig. 78).—Into the duodenum there were

Fig. 78.



Secretion of bile before and after mercuric chloride (corrosive sublimate) given without bile. *a* $\frac{1}{20}$ grain, *b* $\frac{1}{15}$ grain, *c* $\frac{1}{15}$ grain, *d* $\frac{1}{20}$ grain, *e* $\frac{1}{15}$ grain, *f* $\frac{1}{10}$ grain mercuric chloride in 3 cc. water injected into duodenum ($\frac{2}{5}$ grain in all).

injected the following fractions of a grain of corrosive sublimate dissolved in 3 cc. water: $\frac{1}{20}$ at *a*, $\frac{1}{15}$ at *b*, $\frac{1}{15}$ at *c*, $\frac{1}{20}$ at *d*, $\frac{1}{15}$ at *e*, $\frac{1}{10}$ at *f*; two-fifths of a grain being given in all.

NECROPSY.—The mucous membrane of about 14 inches of the upper portion of the small intestine was much congested. In the upper part of the duodenum there were minute hæmorrhagic

extravasations. There was evidence of a very slight purgative effect.

The increase of secretion that followed the fourth dose of mercuric chloride was so slight, that on the whole the result must be regarded as negative. Considering the solubility of mercuric chloride in water,—and the striking contrast between it and calomel in this respect,—it is not at all probable that the negative result in Experiment 78 was due to the non-absorption of the mercurial salt. Possibly it was simply owing to the

Experiment 78A.

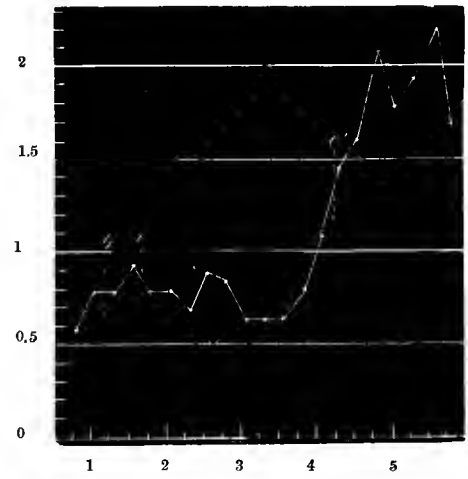
Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.	
0.60	
0.80	
b ——	0.171 cc.
0.80	
0.95	
c ——	
0.80	
0.80	
0.70	
0.90	
0.85	
0.65	
0.65	
0.65	
0.80	
1.1	
c′ ——	
1.45	
1.60	
2.10	
1.80	
1.95	0.472 cc.
2.20	
1.70	

circumstance that, in small—somewhat weak—dogs, such as that employed in the above experiment, the most certain cholagogues sometimes fail to stimulate the liver, probably because of the depressing effect of the preliminary operation adopted in these experiments. At the same time, we resolved in the next experiment to add some bile to the mercuric chloride solution, in case its presence might facilitate absorption, or, at any rate, in order that the conditions encountered in the intestine in a normal case, might be more exactly imitated.

Experiment 78A. Dog that had fasted 19 hours. Weight 16.2 kilogrammes (Fig. 78A).—2.5 cc. water and 0.5 cc. bile were injected into the duodenum at *b*, and $\frac{1}{16}$ grain corrosive sublimate in the same fluid was injected at *c*, and the same dose was repeated at *c'*. At the end of two hours the bile-secretion began to rise, and rose still higher after the second dose.

NECROPSY.—The mucous membrane of the upper 10 inches of the small intestine was decidedly reddened, and there was evidence of a very slight purgative action in this portion of the intestine.

Fig. 78A.



Secretion of bile before and after mercuric chloride given with bile. 0.5 cc. bile and 2.5 cc. water injected into duodenum at *b*. The same fluid with $\frac{1}{16}$ grain mercuric chloride injected into duodenum at *c* and again at *c'* ($\frac{1}{8}$ grain given in all).

Experiment 78B. Dog that had fasted 19 hours. Weight 17.5 kilogrammes (Fig. 78B).—In this experiment the same doses were given and in the same manner as in the preceding experiment. The result was similar, a decided increase of secretion following the second dose.

NECROPSY.—The state of the duodenum and its contents was precisely similar to that described in the preceding experiment.

Experiments 78A and 78B prove conclusively, and in a very striking manner, that mercuric chloride is a hepatic stimulant;

and that it is a powerful one is shown by the fact that in Experiment 78A, $\frac{1}{8}$ grain raised the bile-secretion per kilogramme of body-weight to 0.472 cc. per hour; while in Experiment 78B. it raised the secretion to 0.557 cc. per kilogramme per hour.

Experiment 78B.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.85		*c′*——	
0.80		1.70	
0.80		1.70	
b ——		2.10	
1.05	0·202 cc.	2.15	
0.90		2.55	
0.80		2.15	
c ——		2.40	
0.95		2.35	
1.00		2.80	0.557 cc.
1.10		2.20	
1.20		2.40	
1.30			

The contrast between the last two experiments with mercuric chloride and those with calomel is remarkable, both as regards the effect on the *liver*, and on the *intestine*; for, while the mercuric chloride powerfully excited the liver, but scarcely affected the intestinal glands, notwithstanding its immediate contact with the latter, the calomel did not stimulate the liver, but did powerfully excite the intestinal glands.

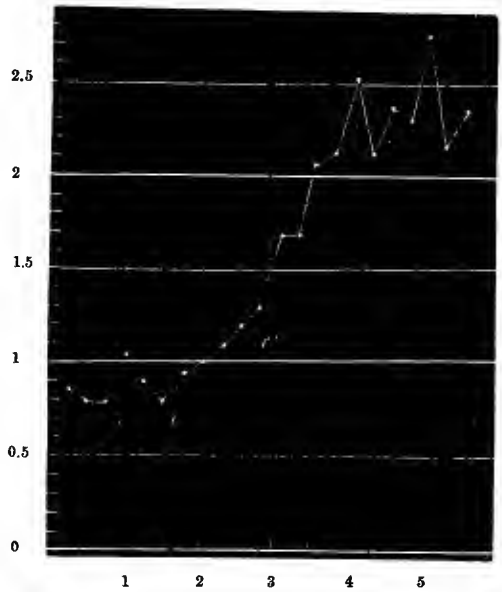
This startling result, so clearly established by these experiments, is a striking proof of the value of this method of investigation as an auxiliary to clinical observations on man.

To render these experiments still more complete, we in the next two cases injected into the duodenum a minute dose of mercuric chloride along with calomel and bile. These experiments are valuable in showing the very remarkable stimulation of the liver that followed an unusually small dose of the mercurial.

Experiment 78C. Dog that fasted 17 hours. Weight 9.9 kilogrammes (Fig. 78c).—0.5 cc. bile and 2 cc. water were

injected into the duodenum at *b*, and $\frac{1}{20}$ grain of corrosive sublimate and 1 grain of calomel in the same fluid were injected at *m*.

Fig. 78B.



Secretion of bile before and after mercuric chloride given with bile. *b*, *c*, and *c'* indicate precisely the same as in fig. 78A.

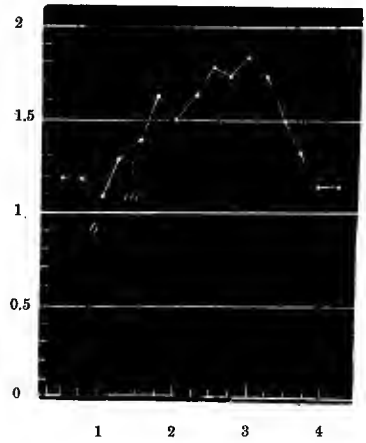
Experiment 78C.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
1.2		1.65	
1.2		1.80	
b ——	0.48 cc.	1.75	0.72 cc.
1.1		1.85	
1.3		1.75	
m ——		1.50	
1.4		1.35	
1.65		1.15	
1.50		1.15	

NECROPSY.—Slightly increased vascularity of mucous membrane of duodenum. No purgation.

In the above experiment, the bile-secretion per hour rose to 0.72 cc. per kilogramme of body-weight, but the secretion was

Fig. 78c.



Secretion of bile before and after mercuric chloride and calomel given with bile. 0.5 cc. bile and 2 cc. water injected into duodenum at *b*. $\frac{1}{20}$ grain mercuric chloride and 1 grain calomel in the same fluid injected into duodenum at *m*.

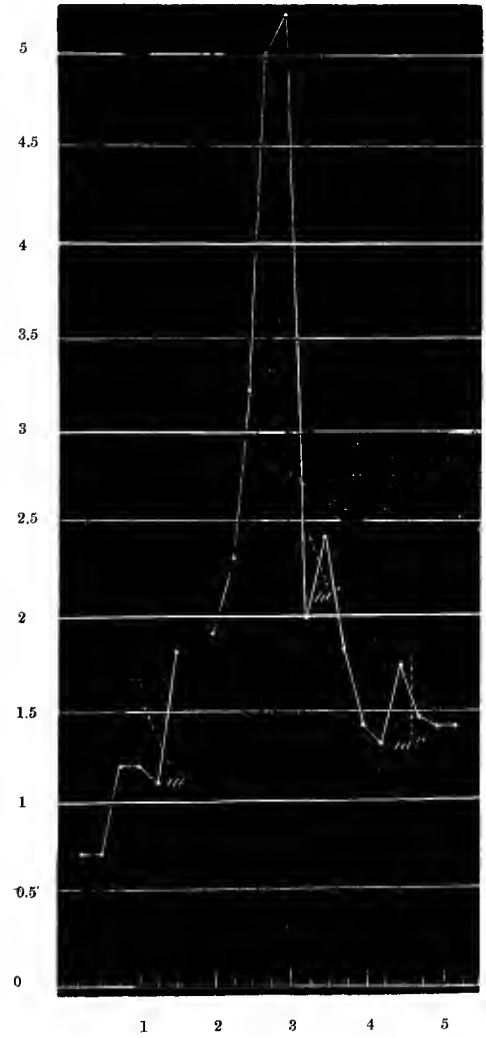
Experiment 78D.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog: per hour.
cc.		cc.	
0.7		2.0	
0.7		*m′* ——	
1.2		2.4	
1.2	0.228 cc.	1.8	
1.1		1.4	
m ——		1.3	
1.8		1.7	
lost		*m″* ——	
1.9		1.45	
2.3		1.4	
3.2	0.85 cc.	1.4	
5.0			
5.2			

so high—0.48 cc.—before the drug was given, that it was difficult to know exactly how to regard the very high figure first mentioned. Another experiment was therefore desirable.

Experiment 78D. Dog that had fasted 17 hours. Weight 18.4 kilogrammes (Fig. 78D).—$\frac{1}{20}$ grain of corrosive subli-

Fig. 78D.



Secretion of bile before and after mercuric chloride and calomel given with bile. $\frac{1}{20}$ grain mercuric chloride with 1 grain calomel in 0.5 cc. bile and 2 cc. water injected into duodenum at m, m', and m'' respectively.

mate and 1 grain of calomel mixed with 2 cc. water and 0.5 cc. bile were injected into the duodenum at *m*, and the same dose was repeated at *m'* and at *m''*.

NECROPSY.—Considerable irritation of the mucous membrane of the upper fourth of small intestine. The contents of this portion of the canal indicated considerable purgative action.

The increase of bile-secretion in Experiment 78D is very remarkable, not only for its absolute extent, but also because of the smallness of the dose that occasioned it. The amount of bile secreted per kilogramme of body-weight rose to the very high figure of 0.85 cc. per hour. The effect of so small a dose as $\frac{1}{20}$ grain of corrosive sublimate in this experiment is very remarkable, for the animal was rather larger than those employed in Experiments 78A and 78B, where $\frac{1}{16}$ and even $\frac{1}{8}$ grain had not so powerful an effect. Considering the result of Experiment 76A, it is not in the least likely that the addition of one grain of calomel to the dose of the mercuric chloride had anything to do with the difference in the result. We can only suggest, by way of explanation, that possibly in some cases the liver is more susceptible to a mercurial stimulus than it is in others.

With the mercuric chloride we had given bile in every case save in Experiment 78, and that was the only instance where the result was negative; we therefore thought it desirable to perform another experiment with mercuric chloride given without bile.

Experiment 78E. Dog that had fasted 17 hours. Weight 13.4 kilogrammes (Fig. 78E).—$\frac{1}{8}$ grain corrosive sublimate in 6 cc. water was injected into the duodenum at *c*, and the same dose was repeated at *c'* and *c''*. The liver was stimulated, the coefficient of bile-secretion rising as high as 0.5 cc. But the experiment is inconclusive, for a reason mentioned in the necropsy.

NECROPSY.—The upper fourth of the small intestine contained a considerable quantity of somewhat dark fluid, looking as if bile had been injected. Possibly some bile had, in this case, escaped from the bile-ducts into the intestine during the performance of the operation. The presence or absence of bile would have been determined by testing the fluid for bile-

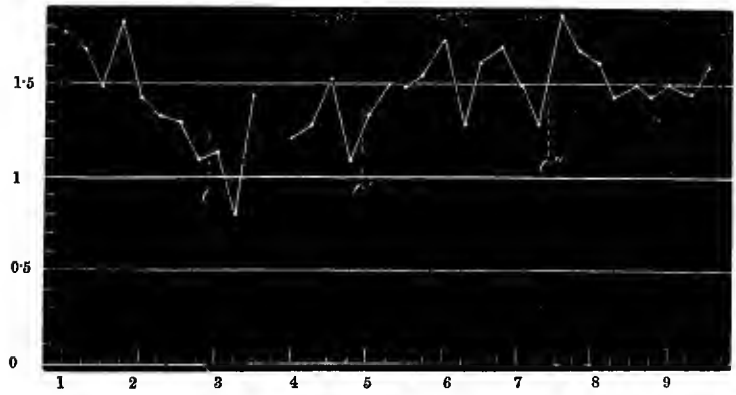
pigment, but unhappily a portion set aside for that purpose was lost.

Experiment 78E.

Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.	Secretion of bile per 15″.	Secretion of bile per kilogramme of dog : per hour.
cc.		cc.	
1.80		1.35	
1.70		1.50	
1.50		1.50	
1.85		1.55	
1.45		1.75	
1.35	} 0.388 cc.	1.30	
1.30		1.65	
1.10		1.70	
c ——		1.50	
1.15		1.30	
0.80		*c″*——	
1.45		1.90	
lost		1.70	} 0.50 cc.
1.25		1.65	
1.30		1.45	
1.55		1.50	
1.10		1.45	
c′——		1.60	

This experiment therefore is inconclusive as regards the point at issue, viz., whether or not mercuric chloride is absorbed from

Fig. 78E.



Secretion of bile before and after mercuric chloride given without bile. $\frac{1}{8}$ grain mercuric chloride in 6 cc. water injected into duodenum at *c*, *c′*, and *c″* ($\frac{3}{8}$ grain given in all).

the intestine without the presence of bile. But we felt that it would scarcely be justifiable to perform yet another experiment to settle the point; for it is to the last degree improbable that bile is necessary, and probably no one will feel inclined to maintain that it is.

TABLE XXV.

Mercury.	Total Dose in Grains.	Grains per kilogramme of Body-weight.	Secretion of bile per kilogramme of Body-weight per hour.	
			Before.	After.
Experiment 78A, Mercuric Chloride,	$\frac{1}{8}$ with bile,	0.0077	0.17 cc.	0.47 cc.
Experiment 78B, Mercuric Chloride,	$\frac{1}{8}$,,	0.0071	0.20 cc.	0.55 cc.
Experiment 78C, $HgCl_2$	$\frac{1}{20}$,,	0.005	0.48 cc.	0.72 cc.
Experiment 78C, HgCl	1 ,,	0.101		
Experiment 78D, $HgCl_2$	$\frac{1}{20}$,,	0.0027	0.22 cc.	0.85 cc.
Experiment 78D, HgCl	1 ,,	0.054		

Result of Experiments with Mercuric Chloride.—These experiments conclusively prove that mercuric chloride is a powerful hepatic stimulant in the dog. Probably—now that attention is specially directed to the subject—it will also be found to stimulate the liver of man; for the experiments already referred to (*Op.* v.), that were carried out by the author for Bennett's committee, showed that the general effects of mercuric chloride on the dog are similar to those observed in man. Doubtless the converse will be found to hold.

In the series of experiments just referred to, on the production of mercurialism in the dog, the mercuric chloride was always injected subcutaneously, and in two experiments on the action of this substance on the biliary secretion, performed for that committee, the drug was given in the same manner. This mode of administering a substance for the purpose of acting on the liver was faulty, and its results are not fairly comparable with those of the ordinary method, where the substance is

placed in the alimentary canal, from which its molecules are absorbed into the radicles of the portal vein, and so pass to the liver in a much more concentrated stream than they possibly can when the substance passes first into the general and then into the portal circulation.

With regard to these two experiments, Hughes Bennett stated in the report (*Op.* v. p. 221) "that corrosive sublimate when given" [*subcutaneously*] "in small doses, gradually increased in strength, does not augment the biliary secretion, but that it diminishes it the moment the dose reaches a strength sufficient to deteriorate the general health." The latter part of the statement was warranted by the results of both experiments. But the first part, though true as regards one of the experiments, was certainly untrue as regards the other (*Op. cit.* p. 212, Table XIII.), where an unequivocal increase of bile-secretion took place when the dose of mercuric chloride, given subcutaneously, was raised from one-sixth grain *once* a day to one-sixth grain *twice* a day (*loc. cit.* June 9th and 10th). The reporter of the experiments on that occasion overlooked the important fact here stated, and deduced the above general conclusion from misleading results, arrived at by taking the daily average quantity of bile secreted during too prolonged a period.

Results of Experiments with Calomel.—With regard to calomel, we have proved the following:—(1.) That calomel in doses of 10 grains, 5 grains, or 2 grains, several times repeated, when placed, *without bile*, in the duodenum of a fasting dog, produces a purgative effect, varying with the dose; but, so far from increasing the secretion of bile, usually diminishes it, just as happens when any other substance that is not a hepatic stimulant—*e.g.* magnesium sulphate—is administered. (2.) That when calomel is *mixed with bile*, and then introduced into the duodenum, there is no difference in the result, even when, as in Experiment 76A, the calomel is given in 1 grain doses several times repeated, and the chance of acting on the liver, previous to supervention of the depressing effect of purgation, thus allowed. (3.) That if 5 grains of calomel be subjected at 100° Fahr. for *seventeen hours* to the action of dilute hydrochloric acid, of the same strength as that of the human gastric juice, not more than $\frac{1}{35}$ grain of mercuric chloride is produced.

The question now arises, seeing that calomel does not usually remain in the human stomach for more than a night, probably not more than from five to six hours, is it likely that even so much as $\frac{1}{35}$ grain of mercuric chloride is produced from the ordinary dose of 5 grains, and if it is, What effect may it be supposed to have on the human liver? It must be borne in mind, however, that we are here on dangerous ground, for we are inclining to reason about the action of the gastric juice itself from experiments on the action of dilute hydrochloric acid, and a solution of alkaline chlorides. It would clearly be more conclusive if we could substitute direct experiment for mere inference. We are in a position to do this.

As regards the dog, it is evident that the only link wanting to complete our chain of evidence is, that we should place the calomel in the *stomach* instead of the *duodenum*, and thus render the case analogous to that of the human subject as regards the administration of this drug. With regard to the cases of calomel, we did indeed seriously think for a time that the negative effect of the calomel on the liver might possibly have been due to the circumstance that the drug was introduced directly into the duodenum, and thus escaped the action of the gastric juice.

Experiment 78F.—Into the stomach of a curarised dog, that had fasted the usual time, we injected 5 grains of calomel in water. The injection was made with a fine syringe, through the *gastric wall*, in order that the whole of it might certainly reach the interior of the viscus. Injection through an œsophagus tube was avoided, because a substance so insoluble as calomel would certainly have clung to the interior of the tube, and would thus have been partly lost.

The result of the experiment was entirely negative, both as regards the liver and the intestinal glands. This was readily explained by the fact, that at the necropsy the calomel was found apparently unchanged, enveloped in the mucus of the stomach. The saliva of the dog is peculiar in containing a very large quantity of mucin. As previously stated (p. 41), the accumulation of this viscous saliva in the stomach during fasting is calculated so seriously to interfere with absorption, that we, on this account, in nearly all these experiments, injected the various drugs directly into the duodenum.

We would not, however, have attempted the preceding experiment, had we at the moment recollected that the question at issue had already received a satisfactory answer from the previous experiments of Kölliker and Müller, Scott, and Bennett's Committee. In those experiments the calomel was given by the mouth in the usual way, and the animals had their usual diet. *Every opportunity was therefore afforded for a transformation of the calomel into mercuric chloride*—probably indeed a better opportunity than is afforded in the human subject, for the gastric juice of the dog is, as previously stated, (p. 146), more acid than that of man,—and yet we find that the action of the calomel, when placed in the stomach of the dog, was just the same as when introduced directly into the duodenum. We have proved that $\frac{1}{20}$ grain corrosive sublimate with 1 grain of calomel when placed in the duodenum (Experiment 78D) can powerfully stimulate the liver of the dog, but we find no reason for entertaining the idea that the amount of mercuric chloride produced by the gastric juice from 5 grains of calomel has any appreciable effect on the liver, for in one of the experiments for Bennett's Committee the amount of calomel placed in the stomach was 10 grains, and it occasioned no increased secretion of bile.*

But it may be said, Although these facts render it impossible to entertain the idea that the action of calomel is due to the mercuric chloride produced from it by the gastric juice, is it not possible that the entire absence of the bile from the intestine in the case of the experiments of Bennett's Committee interfered with the absorption of the drug, so that, while it excited the intestinal glands with which it came directly in contact, it failed to excite the liver because it could not reach it? This objection cannot be entertained—(1.) Because Experiments 76 and 76A of the present series prove that when calomel mixed with bile is placed in the duodenum it does not stimulate the liver. (2.) In the experiments of Bennett's Committee, although the calomel could not possibly encounter bile in the alimentary canal, *a part of it must have been absorbed*, because, when given

[1] The dose of calomel was 10 grains given on three successive days. On the first it produced "slight" and on the other two days "decided" purgation, but on all the days the fluid and the solid bile was diminished.

in small doses, frequently repeated, the animal speedily lost its appetite and became extremely unwell, although the doses were too small to produce purgative action.

The conclusion is inevitable, that while corrosive sublimate does—calomel does not—stimulate the liver of the dog, and that when calomel is placed in the stomach of the dog, there is —if the dose be sufficient—the characteristic action on the intestinal glands, but no excitement of the liver. There is therefore no evidence that a purgative dose of calomel, when acted on by the gastric juice, gives rise to mercuric chloride sufficient to exert any appreciable effect on the liver.

Seeing that in these observations we have submitted to direct experiment on the liver of the dog, every substance that has any reputation as a cholagogue in the case of man, and seeing that we have found that, with the exception of calomel, they all increase the biliary *secretion* in the dog, it appears to us that the remarkable harmony between the vast majority of our results and those of clinical experience, entitles us to maintain that our experiments with calomel are not to be set aside by the clinical observer, merely because he is of the opinion that calomel in some way or other increases the discharge of bile in man. There has been on the part of one or two physicians—who, in their lamentable ignorance and narrow-mindedness, imagine that physiological pharmacology studied on a dog cannot help them to know the action of a drug on man—a tendency to altogether set aside the results of previous experiments with calomel, because they do not harmonise with their previously entertained opinions. These physicians appear to imagine that they can end the discussion by simply saying "the liver of a dog is not that of a man." That truism cannot be disputed, and we are perfectly willing to admit that it is possible that the human liver may be more or less susceptible than the liver of the dog to the influence of various substances, but we maintain that up to this time there *is really no proven discord* between our results and those arrived at by observations on man.

All our experiments have had reference to the secretion and not the expulsion of bile. For the purpose of arriving at *definite* knowledge, we intentionally—in the manner described at the outset of these experiments—threw out of action the *bile-expelling*

mechanism, in order that we might have to deal with the *bile-secreting* apparatus only. *We do not profess to have ascertained anything regarding the action of any drug on the bile-expelling mechanism.*

The clinical observer has supplied most valuable information regarding the power of various substances to increase the amount of bile in the dejections. He observes dejections of a clay colour, he gives five grains of calomel, and further observes that in some cases the dejections thereafter assume their natural appearance. He cannot be certain of the manner in which this result is brought about. For anything he knows, it might be occasioned (1) by stimulation of the hepatic secreting apparatus; or (2) by stimulation of the muscular fibres of the gall-bladder and larger bile-ducts—to wit—the bile-expelling apparatus; or (3) by removing a catarrhal or congested state of the orifice of the common bile-duct, or of the general extent of the larger bile-ducts; or (4) by removing from the intestine substances which had been passing therefrom into the portal vein and depressing the action of the hepatic cells; or (5) by stimulating the intestinal glands, and thus producing drainage of the portal system, whereby the "loaded" liver might possibly be relieved. Yet, notwithstanding the inability of clinical observers to unravel this complicated web, and supply us with any definite statement, one of them [1] has felt inclined to think the results arrived at by Bennett's Committee of no value, because they proved by direct experiment that calomel does not in the dog stimulate the hepatic *secreting apparatus.*

Seeing that calomel stimulates the intestinal glands in the dog as in man; seeing that mercury produces salivation, ulceration of gums, and other characteristic phenomena in the dog as in man, the obvious inference is that the reputed cholagogue action of calomel in the human subject is probably not owing to stimulation of the bile-secreting apparatus. And why should we, in

[1] *Vide* Dr Moxon, *Hunterian Oration*, 1877, *Medical Press and Circular*, March 1877. In that remarkable "oration" Dr Moxon, while adopting an unbecoming style of supercilious criticism of the experiments of Bennett's Committee, showed his ignorance of their object, of the experimental method employed, and of the conclusions drawn. His ignorance of the subject is reprehensible enough in a Hunterian orator, but much more so in a *Lecturer on Materia Medica and Therapeutics* in such a school as Guy's Hospital, London.

the face of our experiments, believe the opposite until the clinical observer substitutes—for *vague conjecture*—definite proof of that opposite, by experimenting in a case of biliary fistula in the human subject, when it happens that no bile enters the intestine, and where the amount secreted may be measured by collecting it as it flows from the fistula.

Our experiments therefore *suggest* that the cholagogue action of calomel in the human subject is to be sought for, not in any supposed power of stimulating the bile-secreting mechanism, but in some one or more of the last *four* modes of action above indicated. Calomel undoubtedly excites the intestinal glands, and for anything we know there may be something peculiar in the nature of its action thereon. For anything we know, it may also have some special influence on the mucous glands and mucous membrane generally of the larger bile-ducts, whereby a catarrhal condition of these ducts may be relieved, and the pent-up bile thus permitted to escape. There is evidently still abundant room for conjecture, but our experiments plainly narrow its range, and thus contribute to the attainment of definite knowledge. The practical physician would, however, do well to observe our discovery, that when a small dose of corrosive sublimate is combined with calomel, stimulation of the liver, as well as of the intestinal glands, is the result. He may probably find it of advantage to apply this combination in the case of man.

SUMMARY OF RESULTS.

1. In a curarised dog that has fasted eighteen hours, the secretion of bile is tolerably uniform during the first four or five hours after the commencement of the experiment, but falls slightly as a longer period elapses. Its composition remains constant.

2. Croton oil is a hepatic stimulant of very feeble power. The high place assigned to it by Röhrig was probably the result of his imperfect method of experiment.

3. Podophyllin is a very powerful stimulant of the liver and of the intestinal glands. During the increased secretion of bile, the percentage amount of the special bile-solids is diminished. If the dose be too large, the secretion of bile is not increased.

4. Aloes in very large doses is a powerful hepatic stimulant. It renders the bile more watery, but at the same time increases the secretion of biliary matter by the liver.

5. Rhubarb is a certain, though not a powerful, hepatic stimulant. The bile secreted under its influence has the normal composition.

6. Senna is a hepatic stimulant of very feeble power. It renders the bile more watery.

7. Colchicum in very large doses is a powerful stimulant of the liver and intestine. It renders the bile more watery, but increases the secretion of biliary matter proper.

8. Magnesium sulphate stimulates the intestinal glands, but not the liver.

9. Castor oil stimulates the intestinal glands, but not the liver.

10. Gamboge stimulates the intestinal glands, but not the liver.

11. Ammonium chloride stimulates the intestinal glands, but not the liver.

12. Scammony is a powerful intestinal but feeble hepatic stimulant.

13. Euonymin is a powerful hepatic but a feeble intestinal stimulant.

14. Iridin is a powerful hepatic stimulant. It also stimulates the intestine, but not so powerfully as podophyllin.

15. Leptandria is a hepatic stimulant of moderate power. It is a feeble intestinal stimulant.

16. Sanguinarin is a powerful hepatic but a feeble intestinal stimulant.

17. Ipecacuan is a powerful hepatic stimulant. It increases slightly the secretion of intestinal mucus; but has no other apparent stimulant effect on the intestine. The bile secreted under the influence of ipecacuan has the normal composition.

18. Colocynth is, in large doses, a powerful hepatic as well as intestinal stimulant. It renders the bile more watery, but increases the secretion of biliary matter.

19. Jalap is a moderately powerful hepatic, and a powerful intestinal stimulant.

20. Taraxacum is a very feeble stimulant of the liver.

21. Dilute nitro-hydrochloric acid is a hepatic stimulant of considerable power.

22. Sodium chloride is a very feeble hepatic stimulant.

23. Rochelle salt is a feeble hepatic but a powerful intestinal stimulant.

24. Sodium phosphate is a powerful stimulant of the liver, and a moderately powerful stimulant of the intestine.

25. Sodium sulphate is a moderately powerful stimulant of the liver, and a powerful stimulant of the intestine.

26. Potassium sulphate is a hepatic and intestinal stimulant of considerable power. Its action on the liver is, however, uncertain, probably owing to its sparing solubility.

27. Sodium bicarbonate has scarcely any appreciable effect as a stimulant of the liver, even when given in very large doses.

28. Potassium bicarbonate does not excite the liver unless it be given in very large doses.

29. Potassium iodide has no notable effect on the biliary secretion.

30. Calabar bean stimulates the liver, but not powerfully, unless it be given in very large doses.

31. Atropia sulphate antagonises the effect of Calabar bean on the liver, and thereby reduces the hypersecretion of bile produced by that substance. It does not, however, arrest the secretion of bile, and, when given alone, does not notably affect it.

32. Menispermin does not stimulate the liver. It slightly stimulates the intestinal glands.

33. Baptisin is a hepatic and also an intestinal stimulant of considerable power.

34. Phytolaccin is a powerful hepatic stimulant. It also slightly stimulates the intestinal glands.

35. Hydrastin is a moderately powerful stimulant of the liver and a feeble stimulant of the intestine.

36. Juglandin is a moderately powerful hepatic and a mild intestinal stimulant.

37. Sodium benzoate is a powerful hepatic stimulant. It is not an intestinal stimulant.

38. Ammonium benzoate stimulates the liver, but not quite so powerfully as the sodium salt of benzoic acid. It does not stimulate the intestinal glands.

39. Benzoic acid stimulates the liver, but, owing to its insolubility, its action is less rapid and much less powerful than that of its alkaline salts.

40. Sodium salicylate is a very powerful stimulant of the liver, but a very slight stimulant of the intestinal glands.

41. Ammonium phosphate is a powerful stimulant of the liver. It does not stimulate the intestinal glands.

42. Tannic acid does not affect the secretion of bile.

43. Acetate of lead, in large doses, somewhat lessens the secretion of bile, probably by a direct action on the liver.

44. Jaborandi is a very feeble hepatic stimulant.

45. Sulphate of manganese does not excite the liver, but it is a powerful stimulant of the intestine.

46. Morphia has no appreciable effect on the secretion of bile, and does not prevent the stimulating effect of such a substance as sodium salicylate.

47. Hyoscyamus does not affect the biliary secretion to any noteworthy extent, and does not interfere with the stimulating effect of sodium salicylate.

48. Pure diluted alcohol does not affect the biliary secretion.

49. Calomel stimulates the intestinal glands, but not the liver.

50. Mercuric chloride (corrosive sublimate) is a powerful hepatic, but a feeble intestinal stimulant. When mercuric chloride and calomel are administered together, both the liver and the intestinal glands are stimulated.

51. The injection of 100 cc. (1543 grains) of water into the duodenum gives rise to only a trifling increase of the bile-secretion (Experiment 6).

52. The injection of 3 cc. (46.2 grains) bile into duodenum does not affect the bile-secretion (Experiments 25, 26); 6 cc. (92.4 grains) increase the secretion slightly (Experiment 10).

53. Purgation produced by purely intestinal stimulants, such as magnesium sulphate, gamboge, and castor oil, diminishes the secretion of bile.

54. When a substance—*e.g.*, podophyllin—which powerfully

stimulates the intestine as well as the liver is given in too large a dose, the bile-secretion may never be increased (Experiment 9), and though it should be increased in the first instance, it is soon diminished as the excitement of the intestinal mucous membrane extends downwards and implicates a larger and larger number of its glands (Experiment 10).

All the above conclusions are based on experiments performed on the dog, and have no reference to any observations made on the human subject.

Although the hourly coefficients of secretion per kilogramme of body-weight before and after the administration of the principal hepatic stimulants have been already given in detail, it will facilitate a comparison of the effects of the different substances if the results be thrown together as in Table XXVI. As already explained, the coefficients of bile-secretion under the influence of hepatic stimulants cannot be regarded as an absolute index of the relative powers of the stimulants, even in the case of the dog, because in some instances—*e.g.*, those of aloes, podophyllin, colchicum, and physostigma—the doses were excessive. It would be unfair to compare the effects of such doses with those of moderate doses of other substances. And, as also has been previously stated, young dogs secrete, in proportion to their size, more bile than old dogs; therefore, a higher coefficient is the rule in their case. We have, as far as possible, taken these points into consideration, and the summary of results above given, contains the conclusions at which we have arrived.

TABLE XXVI.

Experiment.	Substance Given.			Secretion of Bile per kilogramme of Body-weight per hour.	
	Name.	Total Dose in Grains.	Grains per Kilogramme of Body-Weight.	Before.	After.
				cc.	cc.
1	Normal secretion of bile during the influence of small doses of curara,	...	...	0.35	
1A	,, ,, ,,	...	...	0.25	
3	,, ,, ,,	...	...	0.15	
8	Podophyllin,	6, without bile	0.9	0.04	0.47
10	Podophyllin,	4, with bile	0.23	0.52	1.01
11	Aloes,	60, without bile	6.9	0.34	0.69
12	Aloes,	60, ,,	12.0	0.26	0.93
13	Rhubarb,	68, ,,	3.06	0.17	0.32
17	Colchicum,	60, ,,	2.5	0.13	0.45
18	Colchicum,	60, ,,	2.5	0.10	0.20
27	Euonymin,	5, with bile	0.26	0.25	0.47
28	Euonymin,	5, ,,	0.21	0.07	0.46
29	Sanguinarin,	1, ,,	0.05	0.16	0.30
30	Sanguinarin,	3, ,,	0.11	0.12	0.40
31	Iridin,	5, ,,	0.22	0.22	0.53
32	Iridin,	5, ,,	0.92	0.16	0.63
34	Leptandria,	18, ,,	1.10	0.08	0.31
33	Leptandria,	18, ,,	0.88	0.19	0.27
36	Ipecacuan,	60, ,,	2.2	0.24	0.55
37	Ipecacuan,	3, ,,	0.49	0.18	0.38
39	Colocynth,	14, ,,	0.53	0.29	0.45
40	Colocynth,	7, ,,	0.4	0.16	0.27
41	Jalap,	30, ,,	1.2	0.16	0.29
43	Jalap,	40, ,,	3.2	0.17	0.35
60	Dilute Nitro-hydrochloric Acid,	36.4, without bile	2.0	0.11	0.39
53	Rochelle Salt,	463, with bile	37.2	0.23	0.33
51	Sodium Phosphate,	201, without bile	7.4	0.27	0.44
44	Sodium Sulphate,	120, ,,	6.1	0.10	0.27
45	Sodium Sulphate,	508, with bile	32.3	0.25	0.38
50	Potassium Sulphate,	232, without bile	10.7	0.32	0.47
61	Extract of Physostigma	2, with bile	0.0074	0.09	0.36
61A	Extract of Physostigma	2, ,,	0.0147	0.13	0.75
63	Baptisin,	7, ,,	0.303	0.23	0.39
64	Baptisin,	7, ,,	0.374	0.12	0.29
65	Phytolaccin,	2, ,,	0.064	0.144	0.29
65A	Phytolaccin,	2, ,,	0.104	0.338	0.47
66	Hydrastin,	2, ,,	0.077	0.23	0.38
66A	Hydrastin,	2, ,,	0.147	0.09	0.32
67	Juglandin,	5, ,,	0.236	0.10	0.28
		10, ,,	0.472	0.10	0.32
68	Sodium Benzoate,	20, without bile	1.320	0.22	0.64
68A	Ammonium Benzoate,	20, ,,	0.737	0.24	0.54
74A	Sodium Salicylate,	20, ,,	1.000	0.17	0.56
62	Sodium Salicylate,	25, ,,	1.550	0.26	0.66
69	Sodium Salicylate,	20, ,,	2.150	0.32	0.89
78A	Mercuric Chloride,	$\frac{1}{8}$, with bile	0.0077	0.17	0.47
78B	Mercuric Chloride,	$\frac{1}{8}$, ,,	0.0071	0.20	0.55
78C	$HgCl^2$,	$\frac{1}{20}$, ,,	0.005	0.48	0.72
	HgCl,	1, ,,	0.101		
78D	$HgCl^2$,	$\frac{1}{20}$, ,,	0.0027	0.22	0.85
	HgCl,	1, ,,	0.054		

Mode of Action of Hepatic Stimulants.

Although we have definitely proved that a large number of substances stimulate the liver to secrete more bile, we do not profess to have absolutely shown in what manner they do this. It may be asked—

1. Do they excite the mucous membrane of the duodenum or other part of the small intestine, and thereby induce reflex excitement of the liver? One would be readily disposed to entertain this idea from the fact that stimulation of the oral mucous membrane so readily induces secretion in the salivary glands; yet we are obliged to reject the idea that this likewise holds true of the liver, because such substances as gamboge and magnesium sulphate powerfully irritate the intestinal mucous membrane, while they do not in the least increase the secretion of bile. On the other hand, such substances as ipecacuan, sodium benzoate, and ammonium benzoate, powerfully excite the liver without inducing any notable excitement of the intestine.

2. Do these substances stimulate the hepatic cells by merely increasing the stream of blood through the liver? Whatever be the state of the hepatic vessels during increase of the biliary secretion, it is quite certain that increased secretion of bile does not necessarily follow dilatation of the intestinal capillaries, the effect of which, if it be not carried to excess, may with reason be supposed to increase the stream of blood through the portal vein, and thence through the liver. But castor oil greatly dilates the intestinal capillaries, yet the bile-secretion does not rise in the least.

3. We therefore believe that the effect of hepatic stimulants is to be assigned to a direct action of their molecules upon the hepatic cells or their nerves. The effect of physostigma and atropia rather points to an action on the latter—in their instance at all events—as has been already indicated (p. 96). But we do not think it advisable at present to pursue this difficult subject, which, as far as we can see, is of little importance compared with knowing what does and what does not stimulate the liver.

It is particularly to be observed that all our experiments con-

cern the influence of substances on the *bile-secreting* mechanism. The nature of our method has forbidden any observations on the action of drugs on the *bile-expelling* mechanism. Seeing that the acid chyme, by irritating the duodenal mucous membrane, effects a reflex expulsion of bile, it may be that many substances which stimulate the duodenum have a similar effect. Yet we cannot but think that to bring about an *expulsion* of bile by muscular contraction of the gall-bladder and bile-ducts is, in all probability, a small thing when compared with increasing the secretion of bile. One might expect that such powerful intestinal irritants as magnesium sulphate and gamboge would be likely to bring about a reflex expulsion of bile; yet no one has attributed any cholagogue power to these. But, without attempting to reason out a question that can only be determined by experiment, we would merely add, that we leave the investigation of the action of drugs on the *bile-expelling* mechanism to those who care to enter upon such an inquiry. We are satisfied to have shown that every substance supposed to be a cholagogue has, with the exception of calomel (p. 157) and sulphate of manganese (p. 127), the power of exciting the *bile-secreting* mechanism; and, as our estimate of their powers, from an observation of the *bile-secretion* only, so closely agrees with observations on the human subject, where actions on the bile-secreting and on the bile-expelling mechanisms cannot be distinguished from one another, we cannot but infer that surely their actions on the human subject must be chiefly on the bile-secreting mechanism.

The term cholagogue is of necessity a vague one, and is applicable to any substance that increases the biliary flow, whether by augmenting bile-secretion or by exciting contraction in the walls of the bile-passages. We have, therefore, applied the more definite term *hepatic stimulant* to those substances which we have proved to increase the *secretion* of bile.

Hepatic Depressants.

It cannot fail to strike the reader as a remarkable fact that while in the long lists of drugs whose hepatic effects we have

investigated, we have found so many that stimulate the liver, there is only one—acetate of lead (p. 121)—which appears to have a directly depressant effect. We have, however, found several drugs that have an indirectly depressant action; thus, when the intestinal glands are excited to secrete, there is an indirectly depressant effect on the liver, whereby the bile-secretion is lessened. This we have seen to happen when magnesium sulphate, castor oil, gamboge, and calomel are given, and doubtless other purely intestinal irritants have a similar effect. We invariably observed that, while slight purgation—by a purely intestinal irritant—scarcely, if at all, depressed the secretion of bile, powerful purgation produced a very marked effect. Why is the action of the liver thus depressed? In our experiments, we had to deal with fasting animals, whose intestinal canals contained neither bile nor food. Under such conditions, magnesium sulphate could not depress the bile-secretion by diminishing the absorption of substances that augment the formation of bile. Its depressant effect seems, therefore, attributable either to a drain from the portal blood of bile-forming substances, or to an excessive lowering of the blood-pressure in the liver, as in the system generally, by a large dilatation of intestinal and mesenteric vessels. But when such a purely intestinal stimulant as magnesium sulphate is given to an individual under ordinary circumstances, it doubtless depresses the secretion of bile, not only in the manner just indicated, but also by hurrying out of the intestinal canal substances which would otherwise have been absorbed, and would have assisted in the formation of bile. Thus it cannot be doubted that, when the bile is prevented from entering the intestinal canal, less bile is secreted by the liver; and there is ample reason for believing that about $\frac{7}{8}$ths of the sulphur daily secreted by the liver is re-absorbed from the intestinal canal by the portal vessels—in the form of some sulphur-containing substance derived from the decomposition of taurocholic acid—the sulphur-containing acid of the bile. *And it may be that, in abnormal states of the intestinal contents, various deleterious matters may be absorbed, and hamper hepatic action.* Therefore, it is reasonable to suppose that a purely intestinal stimulant, such as magnesium sulphate, although it does not stimulate the liver, may nevertheless in

some abnormal conditions exercise an important influence on that organ, by removing deleterious matters from the intestinal canal, and by draining the portal system. We believe, then, that by the discovery of the depressant effect on hepatic action of purely intestinal purgatives, we have furnished the physician with a fact which will not fail to be of service in rational therapeutics.

Concluding Observations.

In the introduction we pointed out what had been ascertained regarding the actions of drugs on the secretion of bile by our predecessors. We showed that, for want of a proper method of experiment, the definite knowledge arrived at was very meagre, and to some extent erroneous; and, if the statements in that introduction be compared with our summary of results, some idea may be formed of the extent of our labour, which we have striven to render as complete and as free from error as possible. We claim that, by means of a novel and precise method of investigation, we have been the first to place the whole subject of the physiological actions of drugs on the bile-secreting function of the liver upon a sound footing, and thus to lay a real foundation for the rational—that is, scientific—treatment of many diseased conditions of this important organ; and it is gratifying to know that, in consequence of this research, many physicians have been led to use new remedies to which we have specially directed attention. We have indeed occasioned, by our experiments, a considerable amount of pain to a number of dogs; but, considering that our discoveries are calculated to relieve much suffering, not only of men, but also of dogs, for all time to come, we believe that we have spared infinitely more suffering in the future than we have occasioned in the present.

In conclusion, I have to tender my warm thanks to my former pupils, M. Vignal and William J. Dodds, M.B. D.Sc., for their valuable assistance in the performance of the experiments, and for their company during the long and weary hours through which they daily extended. I have very cordially to thank the Scientific Grants Committee of the British Medical Association for having voted upwards of £200 from the funds

of the Association to defray the very heavy expenses incurred for the materials for the research, and for their energetic and powerful support at a time when the clamour of blind ignorance and silly prejudice seriously menaced and almost arrested the progress of this research. Having personally devoted not less than 1400 hours of severe labour to the accomplishment of this work, and having (as, of course, every medical man thinks himself bound to do for the alleviation of suffering) communicated to all every fact calculated eventually to cure affections so common as those of the liver, it is, to say the least, ungrateful, that a certain section of the public should have rewarded our unselfish efforts to cure their hepatic derangements by a flood of abuse; because, like most of our medical brethren, we believe that to be penny-wise and pound-foolish as regards pain is a policy as short-sighted, as narrow-minded, and as reprehensible here as elsewhere. Though profuse with their ingratitude, I doubt not that one and all of them will be very ready and eager to profit by the results of our labour; for I suspect that most of them are scarcely willing to refuse all medical aid, and to thus push their logic to its practical issue. Desiring, as I think most of them do, to continue in receipt of all the medical assistance they can obtain, it may possibly satisfy their conscientious scruples to vainly attempt to make it appear that "*nothing worth knowing*" in medicine has been learned from experiments on animals. It is not difficult, by misrepresentation and by a multiplicity of words, to deceive a public ignorant of the machinery of life and of the processes by which its movements are studied and remedies found for its disorders; but they cannot thus deceive any moderately well-informed and right-minded medical practitioner. The discourtesy, misrepresentation, and injustice that we have suffered at the hands of those who should have acted otherwise, has not, however, induced us to prove false to the interests of suffering humanity. We are conscious of having faithfully done our utmost to advance the scientific treatment of diseases of the liver, and, while steadily pursuing this great object, we have been most careful to avoid the infliction of all pain that was not absolutely necessary.

REFERENCES.

1. H. Nasse: "Commentatio de bilis quotidie a cane secreta copia et indole," Abstract in *Canstatt's Jahresbericht*, 1858, Heft. i. p. 155.
2. Kölliker and Müller: "Beitrag zur Lehre von der Gallen," Würzburg Verhandlungen, 1855, Band v. p. 231.
3. Mosler: "Untersuchungen über den Übergang von Stoffen aus dem Blute in die Galle," *Virchow's Archiv*, 1858, Band. xiii. p. 29.
4. Scott: "On the Influence of Mercurial Preparations on the Secretion of Bile," *Beale's Archives of Medicine*, vol. i. p. 209.
5. Hughes Bennett: "Report on the Action of Mercury on the Biliary Secretion," *British Association Reports*, 1868.
6. Röhrig: "Experimentelle Untersuchungen über die Physiologie der Gallenabsonderung," *Stricker's Jahrbücher*, 1873.
7. T. R. Fraser: "Report on the Physiological Action of Medicinal Substances," *Journal of Anatomy and Physiology*, vol. v. p. 393.
8. Garrod: *Materia Medica*, edited by Baxter, 4th ed. 1874.
9. W. Stewart: "On Chloride of Ammonium in the Treatment of Hepatic Disease," *Philadelphia Medical Times*, January 1878; also in *British Medical Journal*, 28th September 1878.
10. Wood and Bache: *United States Dispensatory.* New York, 1869.
11. H. C. Wood: *A Treatise on Therapeutics.* Philadelphia, 1874.
12. R. Christison: *A Dispensatory.* Edinburgh, 1848.
13. W. Stephenson: "On the Action and Uses of Phosphate of Soda in Small Doses," *Edinburgh Medical Journal*, 1867, xiii. p. 336.
14. B. Keith: *Handbook of Practice.* New York, 1876.
15. Kühne and Hallwachs: "Über die Enstehung der Hippursäure nach dem Genusse von Benzoesäure," *Virchow's Archiv*, Band. xii. p. 386.
16. Meissner and Shepard: "Untersuchungen über das Enstehen der Hippursäure im thierischen Organismus." Hanover, 1856.
17. Schmiedeberg and Bunge: "*Über die Bildung der Hippursäure. Archiv für Experimentelle Pathologie*," Band. vi. p. 233.
18. Husemann: *Die Pflanzenstoffe.* Berlin, 1871.
19. Pareira: *Materia Medica*, 3rd ed. London, 1848–1853.
20. Headland: *The Actions of Medicines*, 4th ed. London, 1867.