to combine it with adequate ventilation. In the case of young or sick children, in which a light might have to be turned on during the night, this usually resulted in curtains being drawn and windows closed throughout the night. In newborn nurseries it was particularly difficult to eradicate recurrent infection while curtains were in use.

In spite of the measures taken for evacuation, many children remained with their parents in London or other danger areas, while some at least of the reception areas were also subject to air attack. During the periods of intense bombardment, children would sleep every night for weeks in crowded air-raid shelters, or be roused from sleep and taken down to the shelters when the alarm was given. In any case, loss of sleep over long periods, overcrowding in a vitiated atmosphere, continual contact with adult anxiety, and the risk of cross infection were inevitable. More thoughtful parents have complained that one of the worst features of this and other forms of overcrowding during the war was that every anxiety was discussed before children, and that circumstances made respect of personal privacy impossible.

In conclusion, I should like to refer briefly to two of the measures to sustain child health which were undertaken during the war. The first is the National Milk Scheme, and the second the provision of school meals on a scale which had never previously been contemplated. The aim of the first was to make safe milk freely available to children and expectant and nursing mothers irrespective of income level. Since the supply of liquid milk inevitably deteriorated owing to the dislocation of rail and motor transport, reduction of agricultural manpower, and limitation of feeding stuffs, the government undertook the production of a full cream national dried milk to be supplied to the priority groups indicated at the rate of 10½d (approximately 18 cents) per tin, representing 7 imperial pints of reconstituted milk, reinforced with vitamin D. This price is less than a fifth of that of many of the corresponding proprietary brands in England. The milk could also be supplied free of cost in necessitous cases. In addition, vitamin supplements (vitaminized oil of peanut and concentrated orange juice or black currant purée) were supplied through the infant welfare centers.

The provision of milk and midday meals in schools aimed at making it possible for all school children to obtain an adequate meal at minimal cost. The value of this, particularly for children traveling long distances to school, or when the mother was employed and unable to cook a midday meal, was not only great to individual children, but communal feeding proved a considerable saving in allocation of a restricted food supply. In many secondary schools in country areas it was possible for the boys to be taught gardening and to produce the necessary vegetables, and for girls to learn to cook and

serve the meals. The available evidence suggests that in at least some urban areas the mean height and weight of elementary school children actually improved rather than deteriorated during the war years, and though this would not apply to all classes of the community, it illustrates what can be done with a restricted food supply when it is equitably and economically distributed.

DIAGNOSTIC ERRORS IN CARCINOMA OF THE LARGE INTESTINE*

Raymond J. Jackman, M. D., M. S. in Proctology, Section on Proctology: Many carcinomas of the large intestine become far advanced before a diagnosis is made, even though accurate diagnostic procedures exist. It is remarkable that many patients, during the period of their symptoms, receive treatment for some supposed condition of the rectum or colon other than the carcinoma, which thus remains undiscovered.

The records of all patients with carcinoma of the colon and rectum who came to the Clinic during a one year period—that is, from January 1, 1944, to January 1, 1945—were studied. There were 817 patients in the group who had a total of 825 lesions; 492 of the patients were males and 325 were females, a ratio of 3:2. The study consisted of considerations of (1) how many carcinomas of the large intestine within reach of the examining finger are diagnosed as, and treated for, some other condition during the course of the patient's symptoms, the carcinoma remaining undiscovered; (2) how many additional carcinomas which should have been visible at sigmoidoscopy are erroneously treated, and the nature of the treatment; (3) how many carcinomas discernible in roentgenograms of the colon likewise are erroneously treated, and the nature of the treatment; and (4) how many carcinomas of the large intestine are discovered only at surgical abdominal exploration.

LESIONS ACCESSIBLE TO EXAMINING FINGER

Of the entire group of 817 patients in this study, 634 or 77.6 per cent had carcinomas which were located in the terminal portion of the bowel, meaning the sigmoid, rectum and anorectal region. The lesions of 444 patients (70 per cent of the 634 who had lesions of the terminal part of the bowel or 54.3 per cent of all those who had carcinomas of the large intestine) were palpable on digital examination, or were within reach of the examining finger. Many of the lesions of the sigmoid were palpable in the form of extrarectal masses, and actually were suspected rather than being directly palpable.

*Abstract of paper by Jackman, R. J., Neibling, H. A. and Waugh, J. M.: J.A.M.A. 134:1287-1289 (Aug. 16) 1947.

Of the 444 patients who had palpable lesions, 102 or 23 per cent of them had received treatment, during the course of their symptoms, other than treatment directed toward the unsuspected carcinoma that later was found to be within reach of the examining finger. Analysis of some of the various therapeutic procedures instituted in this group of 102 patients showed that forty-two underwent surgical treatment for hemorrhoids, and that four of the patients underwent this procedure twice. Another group of thirty-five patients received a form of injection treatment for hemorrhoids. Four patients underwent surgical treatment of fissure; four underwent fistulectomy. Four others underwent some form of anorectal surgical procedure the exact nature of which the patient did not know. Three patients were treated for colitis and three for amebiasis. Another four patients received electrical treatment for hemorrhoids; three others were treated with suppositories. Interesting is the fact that, as previously mentioned, each of four patients underwent two operations for hemorrhoids while they had the symptoms of carcinoma.

LESIONS NOT ACCESSIBLE TO EXAMINING FINGER BUT VISIBLE AT PROCTOSIGMOIDOSCOPY

In addition to the 444 patients (54.3 per cent of all those who had carcinomas of the large intestine) who had lesions palpable on digital examination, all of which were visualized at proctosigmoidoscopy, 132 additional patients or 16.2 per cent had lesions of the lower bowel which were visible by sigmoidoscopy. Thus, a total of 576 patients (70.5 per cent of the total series of 817) had carcinomas of the large intestine which were within reach of the sigmoidoscope.

In this group of 132 patients who had lesions not palpable on digital examination but within reach of the sigmoidoscope, thirty-four or 25.8 per cent had received treatment directed at some condition other than the carcinoma, which had remained undiscovered. An analysis of this group of thirty-four patients showed that twenty-eight patients had been treated either surgically or by some unknown procedure to the anus. One had undergone fistulectomy, three had been treated for amebiasis and two had been treated for ulcerative colitis.

LESIONS DISCERNIBLE IN ROENTGENOGRAMS OF THE COLON

Of the patients who had lesions located higher in the colon, beyond the reach of the examining finger and sigmoidoscope, 232 (28.4 per cent of the total series of 817) had carcinomas which were diagnosed by roentgenograms of the colon. Twenty-three patients or 9.9 per cent of this group had received other treatment during the period in which they were experiencing symptoms from the carcinoma. Six had been operated on for hemorrhoids. Five had been treated for pernicious anemia by the intramuscular injection of liver extract. It is generally accepted that a secondary type of anemia is of common

occurrence in the presence of malignant processes of the right portion of the colon. Five patients had been treated for colitis of some form; two had been treated for amebiasis and two had undergone appendectomy. In the latter two cases the carcinoma had remained undiscovered, even though it was located in the cecal region. Polyps in the rectum had been diagnosed and treated in three patients, but carcinomas situated in a higher segment of the colon had not been discovered. It should be pointed out that the discovery of one polyp or more in the lower bowel ought to be an indication for examination of the rest of the colon by roentgen rays, with which the double contrast method is employed.

LESIONS ENCOUNTERED AT SURGICAL ABDOMINAL EXPLORATION

The remaining nine (1.1 per cent of the total series of 817) patients had lesions that had been diagnosed only at surgical abdominal exploration. In most instances in this group, performance of emergency colostomy had been necessary because of obstruction of the large bowel, and the diagnosis had been made at the time of that operation. No significant treatment had been carried out for members of this group during the period in which they had experienced symptoms from carcinoma.

COMMENT

Paradoxic as it may seem, results of this study would indicate that those patients who have carcinomas of the large intestine which can be diagnosed with the greatest ease—that is, by digital examination only—are more likely to be treated for some condition unrelated to the carcinoma. Of the 444 patients, or 54.3 per cent of the total of 817, who had lesions palpable on digital examination of the rectum, 102 (23 per cent of the 444), or one of every four, had received some other treatment not directed at the carcinoma during the period in which they were experiencing symptoms from the unsuspected carcinoma. In comparison to this, of the 232 patients who had lesions located at a higher level in the large intestine, twenty-three or 9.9 per cent of the 232 had been treated for some other condition, while none of the thirteen patients who had carcinomas diagnosed at surgical abdominal exploration had received treatment for the lesion in question.

CONCLUSIONS

More than half (54.3 per cent) of all patients with carcinoma in any part of the large intestine in the group studied had lesions which could be palpated by digital examination of the rectum. About a fourth (23 per cent) of the patients in this group had received some form of treatment for disease of the colon or rectum, but not for carcinoma, during the course of their symptoms arising from the unsuspected carcinoma that was within reach of the examining finger.

An additional 16.2 per cent of all the patients who had carcinomas anywhere in the large intestine had lesions which were within reach of the sigmoidoscope. A fourth (25.8 per cent) of this group had received treatment for some condition other than the carcinoma, which had remained undiscovered.

Patients who had carcinomas of the large intestine that were beyond the reach of the examining finger and sigmoidoscope constituted the remaining 29.5 per cent of the total series of 817. Of this group of 817, 28.4 per cent had carcinomas that were diagnosed by roentgen-ray studies of the colon, and 1.1 per cent had lesions that were discovered at abdominal surgical exploration. In this group, during the period of symptoms from carcinoma, only 9.9 per cent of the patients had received treatment directed toward any other condition.

RAYNAUD'S DISEASE: REPORT OF CASE WITH LATE POSTOPERATIVE RESULTS

Alfred W. Adson, M. D., Section on Neurosurgery: The medical history of the patient whose case I am reporting has several interesting features. First, the symptoms of Raynaud's disease began at the age of twelve years. Second, at the age of sixteen years the patient underwent bilateral lumbar sympathectomy, and was the first patient to my knowledge on whom the operation was performed for Raynaud's disease of the lower extremities. Third, the results of the lumbar sympathectomy in January, 1946, twenty years and ten months following the operation, were just as good as they were immediately after operation and there were no signs of recurrence.

The patient was admitted to the Clinic on March 10, 1925, when she was sixteen years old. Her complaint was pain in the calves of her legs, feet and knees when she stood or walked. She was unable to walk more than three or four blocks because of the severe pain. This was worse during the winter months, and because of the pain she never had been able to enjoy skating or bobsledding.

From the medical history, it was learned that the patient had been well until the age of six years when scarlet fever developed. At the age of ten years, her feet would swell and would become painful. There was no Raynaud's type of discoloration until she was thirteen years old. An ulcer, however, would recur on the left big toe during the winter months.

During the three years previous to admission to the Clinic her symptoms gradually progressed until she was completely incapacitated. Findings revealed that she was suffering from true Raynaud's disease which involved all the extremities, but her lower extremities were involved to a greater extent than the upper extremities. All the color changes would take place. The extremities would become white, then

cyanotic and finally red and edematous. All peripheral blood vessels were patent. A scar was present on her left big toe. Physical examination otherwise and laboratory studies gave negative results.

The real problem was to outline a course of treatment. Attempts at medical management had been carried on for three years previous to admission. Though Leriche's operation, periarterial sympathectomy, for Raynaud's disease offered a limited amount of ineffective relief, it was apparent a sympathectomy of wider scope had to be devised.

At this time, the late Dr. George Brown was studying the skin temperatures and elimination of heat in a group of patients on whom I had performed bilateral lumbar sympathectomy for spastic conditions of the lower extremities. The Stewart-Keggeris calorimeter revealed a marked increase in the elimination of heat following bilateral lumbar sympathectomy. This observation compelled me to conclude that the more extensive bilateral lumbar sympathectomy had resulted in a greater flow of blood through the sympathectomized blood vessels than through the blood vessels on which the periarterial sympathectomy of Leriche had been performed.

Although the transabdominal bilateral lumbar sympathectomy had not been previously performed for Raynaud's disease, I believed that it was indicated in view of the observations made on patients who had spastic conditions. On March 19, 1925, I performed such a procedure on the patient. In the sympathectomy were included the second, third and fourth lumbar ganglia and the intervening trunks on both sides in order to interrupt all preganglionic and postganglionic sympathetic fibers to the arteries of the feet and legs. I also stripped off the adventitious coat of both common iliac arteries, a procedure I discontinued shortly because it was unnecessary and added nothing to the effectiveness of the sympathectomy.

The postoperative results were dramatic. Convalescence was uneventful. Three weeks after operation, just before returning home, the patient walked eleven blocks in cool April weather in order that Dr. Brown and I could present her and her story to the Clinic staff. All symptoms referable to the feet and legs had disappeared. The skin of the feet and legs was warm, pink and dry. She could stand and walk without discomfort. The laboratory studies disclosed a marked increase in skin temperature and an absence of sweating of the feet and legs which corresponded to the dermatomes affected by the sympathectomy. Color changes of the hands continued to take place, although they were less severe and were never accompanied by trophic ulcers or pain. Therefore, sympathectomy for the hands was not advised during her first visit to the Clinic.

I have had occasion to see this patient several times during the intervening years, but the opportunity to determine the skin temperatures and the distribution of sweating had not presented itself until

January, 1946. Studies were made by Dr. Grace Roth and are herein included (fig. 1). Color changes still occurred in the hands; fortunately for the patient they were not accompanied by pain or trophic changes. Therefore, a cervicothoracic sympathectomy has not been advised.

The skin over the feet and legs was pink in color and much warmer than the skin of the hands. Symptoms referable to the lower extremities have not recurred. The skin which was void of sweat is very dry but not broken. The patient stated that she has treated the dry skin with an oily ointment. During these many years she has been free from pain in the legs and has been able to walk as much

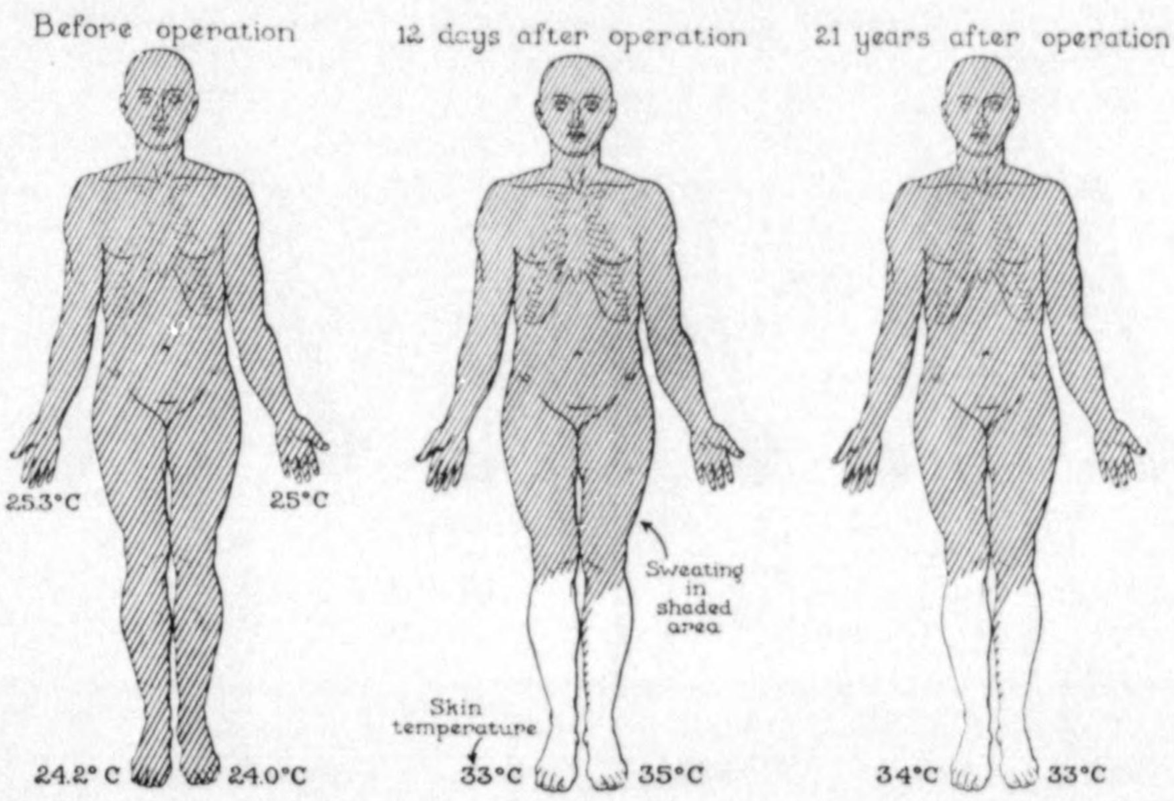

Fig. 1. Skin temperatures and distribution of sweating before and after bilateral lumbar sympathectomy. The changes which occurred after sympathectomy have been maintained for twenty-one years.

as she liked, except for two periods. The one occurred when phlebitis with varicose veins developed after the birth of her second child, and the second time occurred after operation for varicose veins of the legs.

Another interesting point in the history supports the opinion that an autonomic unbalance affecting one part of the body may also affect other parts since the patient had had recurrent symptoms from a duodenal ulcer for the past thirteen years. These symptoms made her return for operation which Dr. B. M. Black performed. He resected the pyloric end of the stomach. Her recovery after this operation has been just as rapid and effective as it was after sympathectomy.

PRELIMINARY REPORT ON EXPERIMENTAL AND CLINICAL STUDIES WITH POLYTHENE FILM*

M. Hunter Brown, M. D., Fellow in Neurosurgery, Mayo Foundation, John H. Grindlay, M. D., M. S. in Surgery, M. S. in Experimental Surgery, Division of Experimental Medicine and W. McK. Craig, M. D., M. S. in Surgery, Section on Neurologic Surgery:

The effort to find an adequate substitute for the dura mater when this membrane has to be sacrificed because of injury or disease has occupied investigators for many years. The voluminous list of materials employed is perhaps a testimonial to some of the difficulties that have been encountered. These substitute materials, in general, fall into four groups: (1) the metallic foils, such as gold, silver, platinum and tantalum, (2) the autoplastic membranes, such as fascia lata, periosteum, peritoneum and fatty tissue, (3) the nonviable membranes, such as amniotic membrane, allantoic membrane and Cargile membrane and (4) a group of miscellaneous materials, including celluloid, cellophane, fibrin film and rubber tissue.

There is general agreement that the dural substitute should possess the following basic characteristics: (1) inertness in cerebral tissue, (2) nontoxicity, (3) nonresorbability, (4) high tensile strength, (5) elasticity, (6) ability to hold sutures and (7) nonadherence to leptomeninges and cortex.

The materials which have attracted the most attention during the recent war period as dural substitutes are tantalum foil, fibrin film and animal membranes. Although they are valuable adjuncts in certain situations, none of these substances completely fulfill all the criteria for artificial dura. All are notably deficient in ability to hold sutures and have many individual drawbacks with respect to the other properties that have been mentioned. When polythene film became commercially available in quantity and appeared to possess the requisite physical properties for an artificial dura, experimental tests were instituted to determine its suitability.

EXPERIMENTAL STUDIES ON PROPERTIES AND USES OF POLYTHENE†

For the past year and a half polythene has been used at the Institute of Experimental Medicine for the surgical reconstruction of several organs. These experimental studies are still in progress but we do not believe it too early to state that polythene has great promise as a material for temporary or permanent surgical implantation in living tissue. Certainly, it meets the basic requirements which any material for permanent implantation must meet. It does not

*Presented at the meeting of the general staff of the Mayo Clinic on July 14, 1947.
†Supplied by the Visking Corporation, Terre Haute, Indiana.

undergo change when surrounded by living tissue and it produces neither remote nor local body changes.

Polythene, or polyethylene, is one of the more recently developed plastics. It is made by polymerizing, under high pressure, molecules of ethylene. The result is macromolecules consisting of long carbon chains in which each carbon bears two hydrogen atoms. Polythene is simply a glorified paraffin in which the chain molecules are very much longer than in ordinary household paraffin. Like paraffin, polythene is insoluble in, and is not wetted by, water or aqueous solutions. It is unaffected by strong acids and alkalies and by powerful reagents such as fluorine gas.

Unlike paraffin, polythene is completely insoluble in all known solvents at a temperature of 60° C. or less, nor does it melt in boiling water. Polythene is flexible, elastic and much tougher than paraffin, and its softening point is at a temperature greater than that of boiling water (approximately 110° C.). It is light in weight (specific gravity 0.92), conducts heat poorly, is an excellent electric insulator and has a low coefficient of friction. It is transparent to roentgen rays. Polythene has a pearly gray color, but in thin sheets it is transparent and colorless. Unlike cellophane, polythene holds a suture very well; that is, a suture placed near the edge of thin film does not tear out. Other virtues of polythene are that it is cheap, that it is easily sterilized by chemicals or boiling in water and that it is easy to handle. It can be cut to a desired shape with knife or scissors, and by heating it to its molding temperature, one can make molded articles of polythene.

We have found no evidence of reaction, foreign body or inflammatory, when polythene is buried in body cavities or tissues. A method of inserting capillary-size tubing into veins for continuous intravenous administration has already been reported.[1] In some cases it has been possible to keep a solution for intravenous use running through such a tube into the same vein for two weeks. In the near future we shall describe methods of anastomosing the common bile duct, trachea and pelvic colon respectively with molded polythene tubes. Again, in these studies, we have observed no tissue reaction to polythene and no tendency for the plastic to deteriorate or for the tubes to become blocked with secretions or solid material.

In the study we are reporting now the physical characteristics which make polythene suitable for implantation in many tissues and the minimal biologic reaction which we have observed in all our studies were demonstrated.

Ten animals (eight dogs and two monkeys) were employed in the experimental study with polythene film and tubing. All operations were carried out under intratracheal ether anesthesia, sterile technic

1. Guenther, T. A., Grindlay, J. H. and Lundy, J. S.: New flexible capillary tubing for use in venoclysis. Proc. Staff. Meet., Mayo Clin. 22:206-207 (May 14) 1947.

being used. In seven animals large osteoplastic bone flaps were fashioned and a comparable area of dura was excised and replaced with polythene film; in addition, in two of these animals the underlying cortex was lacerated to produce specific neurologic defects. In the remaining three animals polythene tubes were inserted into the lateral ventricles to form an artificial fistula between these cavities and the subarachnoid space. The brains of eight animals have been re-examined at intervals of two, four and six months; the others will be observed indefinitely for possible late deleterious effects. Wound healing has been normal in all instances, and there have been no deleterious neurologic effects attributable to the artificial dura. In the two instances in which the cortex was lacerated beneath the film, recovery of sensory-motor function proceeded at the anticipated rate. All ventriculostomy tubes have been re-examined and found to be patent and unchanged in appearance.

Examination of the polythene film after removal from the animals showed that it was identical in physical properties with the material in its normal state. The film was entirely nonadherent to the underlying leptomeninges and cerebral cortex, and was surrounded by a small dead space. Grossly and histologically there was a thin subdural neomembrane that had formed between the film and the arachnoid; this was actually a regeneration of the inner layer of the dura mater. The collagenous fibrils of this neomembrane were oriented, in regeneration, in a direction that paralleled the film in the dead space. The neomembrane was likewise nonadherent and was easily dissected off the underlying arachnoid in both the wounded and unwounded animals; there appeared to be no tendency for a downgrowth of fibrils to form a traction cicatrix. Histologic sections have shown no evidence of reaction in the underlying arachnoid, pia and cortex.

CLINICAL APPLICATIONS OF POLYTHENE FILM IN NEUROSURGERY

A preliminary clinical trial of polythene film indicates that the material is a satisfactory substitute for the dura mater when repair or replacement of this membrane is necessary. By utilizing the various properties of polythene, it is possible to facilitate many procedures in the everyday practice of neurosurgery. The film is primarily intended to replace the dura when excision is necessary in invasive tumors, such as meningioma, and to repair dural defects in cerebrospinal rhinorrhea and other spinal fluid fistulas. Subsidiary uses of polythene film which may prove to be of increasing importance are the following: (1) the prevention of meningocerebral adhesion in penetrating craniocerebral wounds, (2) to provide both protection and elasticity for the herniating lobe in subtemporal and suboccipital decompression, (3) in peripheral nerve anastomosis to protect nerve ends and to surround the gap with a tube in two-stage procedures,

(4) the prevention of damage to the arterial intima in ligations for intracranial aneurysm and (5) cosmetic uses, such as the covering of the anterior burr hole in transfrontal craniotomy. Due to the variety of applications of this new material, additional clinical experience is needed to define its scope and usage with greater accuracy.

SUMMARY AND CONCLUSIONS

1. An experimental study with polythene film has shown that it fulfills the criteria of a dural substitute.

2. Polythene film did not adhere to the underlying leptomeninges and cerebral cortex. This property allowed the dura to regenerate between the film and the arachnoid. Histologic sections showed no reaction in the pia-arachnoid and cerebral cortex to the presence of polythene film.

3. The results of a preliminary clinical trial indicate that polythene film is a satisfactory substitute for dura mater when repair or replacement of that membrane is required.

TISSUE ANOXIA RESULTING FROM RESPIRATORY ALKALOSIS

Haddon M. Carryer, M. D., M. S. in Physiology, Division of Medicine: The syndrome of hyperventilation is one of the most common and yet one of the most infrequently recognized medical disorders. This functional derangement of breathing, with the sequelae it precipitates, is often regarded as a manifestation of nervousness, yet when organic disease is simulated by the syndrome of hyperventilation, serious consequences by unwarranted restrictions may result from an erroneous interpretation of a patient's symptoms.

The syndrome of hyperventilation results from excessive loss of alveolar carbon dioxide caused by increased respiration. By reduction of the partial pressure of alveolar carbon dioxide from its usual value of that of 40 mm. of mercury to a value less than half that, respiratory alkalosis is induced in the body.[1] This takes place because of a disturbance in the normal equilibrium between carbon dioxide in the alveoli and that in the blood. The increased alkalinity of the blood, the presence of which is responsible for the symptoms of the syndrome of hyperventilation, results from the loss of carbon dioxide into the surrounding atmosphere.

Persons who are tense, anxious or exhausted are particularly likely to hyperventilate. This may occur because of unrecognized stimulation of the respiratory center with the result that the rate or

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1. Best, C. H. and Taylor, N. B.: The physiological basis of medical practice. Ed. 4, Baltimore, The Williams and Wilkins Company, 1945, pp. 350 and 361.

depth of the respiratory excursion, or both, is increased. Often the syndrome is manifested by frequent, sighing breathing. At times patients feel ill and, not knowing what to do, further hyperventilate by forced breathing in an attempt to overcome the early symptoms of respiratory alkalosis, thus initiating a vicious circle. This often occurs if a patient is in a situation in which embarrassment would be suffered should he faint or become ill. In crowds, in church or in circumstances associated with emotional duress this condition most often occurs. Patients who have a tendency to manifestations of hysteria will frequently hyperventilate as a so-called trigger mechanism in the production of their hysterical reaction.[2]

The symptoms of the syndrome of hyperventilation represent a sequence of events first evidenced as symptoms of anxiety, such as giddiness, lightheadedness or confusion. The symptoms are all subjective. As the symptoms progress, although the patient has been overbreathing, a sense of suffocation and of inadequate respiration is experienced. Patients frequently seek to get out-of-doors, open a window or fan themselves. They will state that "the air is doing no good," "I can't get a satisfactory breath," "the air isn't going down far enough" or "I can't get enough air." At this stage of the condition a discomforting sense of vague, dull pressure within the chest is often perceived; this symptom necessitates care on the part of the examining physician to determine whether disease of the coronary artery is present. With further hyperventilation the patient experiences a sensation of tingling or numbness of the extremities and face and may become alarmed over the seeming imminence of some dire happening, such as a stroke or a heart attack. Many patients then may proceed to a tetanic state in which carpopedal spasm, associated at times with stupor, occurs.

Institution of voluntary forced breathing to the extent of causing the disturbing symptoms to appear serves as a useful adjunct in demonstrating to such patients the functional nature of their symptoms and in reassuring them. Instruction as to the cause of the complaint and advice as to control of symptoms by the methods of rebreathing air from a paper sack, of holding the breath, of nasal rather than oral breathing and of avoidance of sighing should be made. The use of these procedures allows reaccumulation of alveolar carbon dioxide and correction of the respiratory alkalosis induced by hyperventilation. The patient is then less reluctant to discuss the emotional factors motivating his anxiety and, consequently, psychotherapy is often more effective.

The respiratory derangement associated with the syndrome of hyperventilation arises as a result of two occurrences. The first is

2. Carryer, H. M.: The role of hyperventilation in functional disorders. Proc. Staff Meet., Mayo Clin. *21*:361-367 (Sept. 18) 1946.

psychogenic stimulation of the respiratory center by nervous reflexes of voluntary or involuntary origin, as indicated previously. The second is that of true anoxia which results in the course of hyperventilation, from inadequate release of oxygen in the tissues of the body. To understand the mechanism by which hyperventilation leads to anoxia of tissues, knowledge of the physiology of transport of oxygen by the blood is necessary.

Hemoglobin carries oxygen in chemical combination.[3] In pure solutions of hemoglobin the reaction takes place in accordance with a manner approaching the law of mass action. Variations in the concentration of oxygen to which hemoglobin is exposed determine

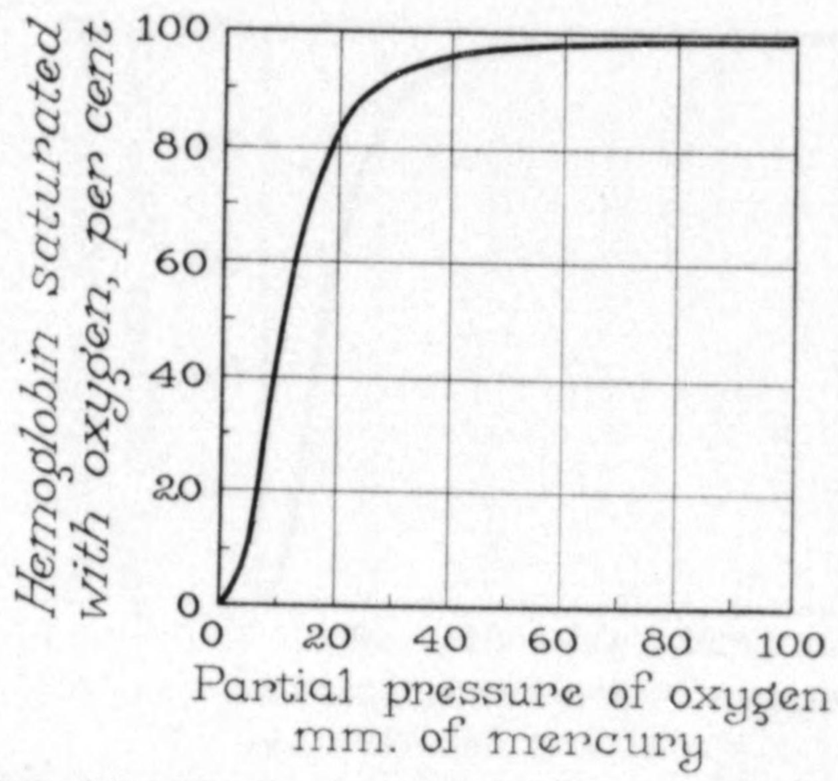

Fig. 1. Curve of dissociation of oxyhemoglobin in the horse. (Modified from Barcroft, Joseph: Quoted in Henderson, L. J.: J. Biol. Chem. *41*:402 (Mar.) 1920.

the proportion of oxygen in actual chemical combination with hemoglobin. Barcroft[3] has illustrated the manner in which such a union takes place by studies made on the hemoglobin of the horse (fig. 1). Partial pressures of oxygen and carbon dioxide given in this paper are measured in millimeters of mercury. It is noted that conditions in the lungs are ideal for the reaction $Hb + O_2 \rightarrow HbO_2$ (in which Hb represents hemoglobin and O_2, oxygen) inasmuch as the partial pressure of oxygen in alveolar air is approximately 100. With the partial pressures of oxygen falling to 40 there is still virtually complete saturation of the hemoglobin with oxygen. It is equally apparent, from observation of the curve of dissociation of oxyhemoglobin, that

3. Barcroft, Joseph: The respiratory function of the blood. Part II. Hemoglobin. Cambridge, The University Press, 1928, chap. XII, pp. 118-133.

conditions would be unsatisfactory for the reverse reaction $HbO_2 \rightarrow Hb + O_2$ in the tissues of the body in which the partial pressure of oxygen ranges below 40 which is the usual partial pressure of oxygen observed in mixed venous blood. If such a curve were indicative of the dissociation of oxyhemoglobin in the tissues, less than 5 per cent, approximately, of the oxygen held by the hemoglobin would be released in tissues with a partial pressure of oxygen of 40 and less than 18 per cent, approximately, in tissues in which the partial pressure of oxygen is 20.

Barcroft has found that certain factors exercise a striking influence on the dissociation of oxyhemoglobin. The effects of changes

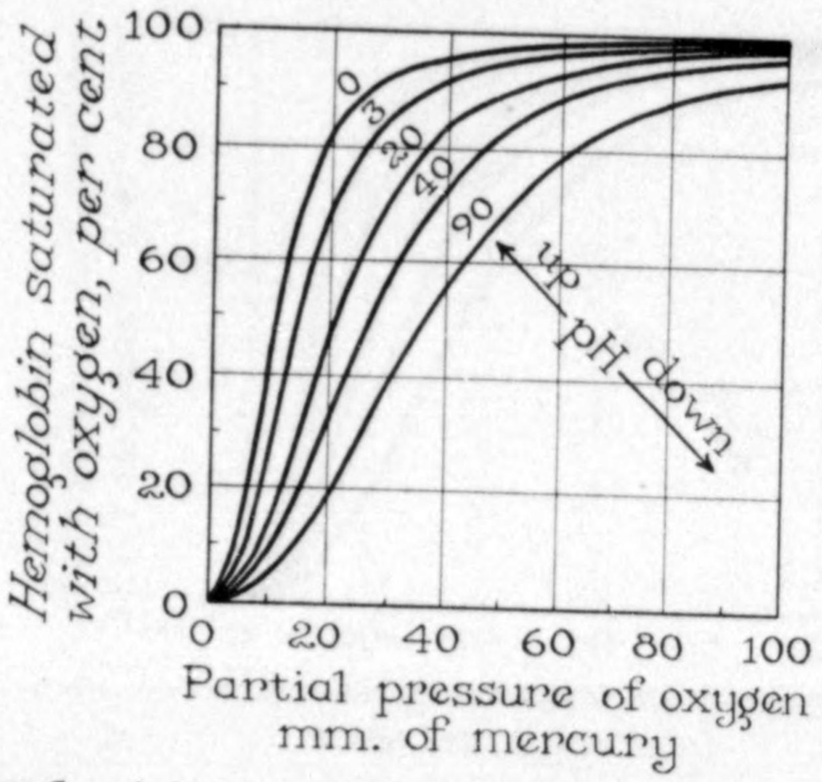

Fig. 2. The effect of changes in the pH of serum, produced by the presence of carbon dioxide at pressures which vary from 0 to 90 mm. of mercury, on the dissociation of oxyhemoglobin in the horse. (Modified from Barcroft, Joseph: Quoted in Henderson, L. J.: J. Biol. Chem. *41*:402 (Mar.) 1920.

in temperature on the reaction of oxygen and hemoglobin can be represented by a curve which becomes somewhat flattened when 37° C. is approached. The presence of sodium or potassium chloride tends slightly to give effects which can be represented by a more rectangular curve. Wide variations in the concentration of hemoglobin will have, for experimental purposes, minor effects on this curve. The most important influence, however, has been found to be that exercised by the concentration of carbon dioxide in the medium in which the reaction takes place.[4] This effect is accomplished not by a specific action of carbon dioxide but by the change carbon

4. Henderson, L. J.: The equilibrium between oxygen and carbonic acid in blood. J. Biol. Chem. *41*:401-430 (Mar.) 1920.

dioxide produces in the hydrogen ion concentration in the blood. The experimental use of acids other than carbonic acid to establish hydrogen ion concentrations of the blood equivalent to those caused by the presence of carbon dioxide brings about similar effects which can be reflected in the curve of dissociation of oxyhemoglobin. The effect of carbon dioxide on the tissues, with the resulting change in hydrogen ion concentration, is the primary factor in forcing the hemoglobin to relinquish its oxygen (fig. 2). For example, when the partial pressure of carbon dioxide is 45, the hemoglobin will relinquish 28 per cent of its oxygen instead of less than 5 per cent

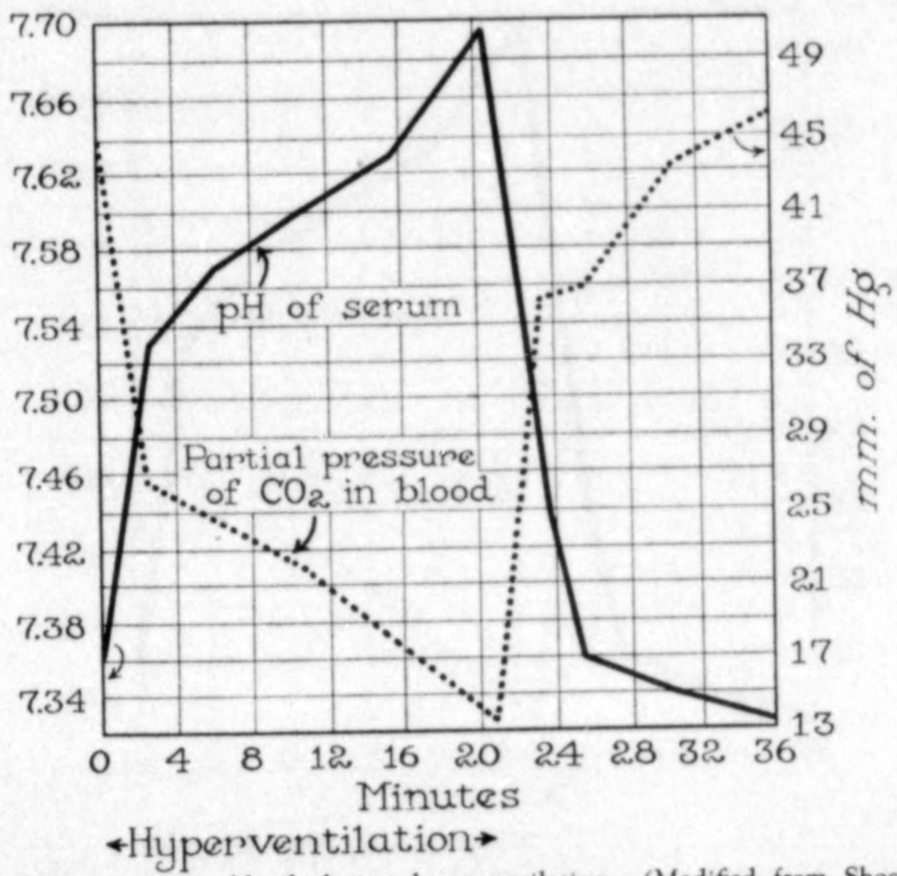

Fig. 3. Changes in the blood during hyperventilation. (Modified from Shock, N. W. and Hastings, A. B.: J. Biol. Chem. *112*:254 (Dec.) 1935.

as would occur in the absence of carbon dioxide, with the partial pressure of oxygen remaining constant at 40. Should the partial pressure of oxygen in the tissue fall to 20, approximately 66 per cent of the oxygen can be released by virtue of the presence of carbon dioxide at a pressure of 45, as compared with only 18 per cent of the oxygen released in the absence of carbon dioxide.

That the hydrogen ion concentration of the serum varies with the tension of the carbon dioxide has been graphically shown by Shock and Hastings[5] (fig. 3) who made twenty-four determinations of the effects of periods of forced breathing on six normal subjects.

5. Shock, N. W. and Hastings, A. B.: Studies of the acid-base balance of the blood. IV. Characterization and interpretation of displacement of the acid-base balance. J. Biol. Chem. *112*:239-262 (Dec.) 1935.

The partial pressure of carbon dioxide in the blood decreased more than 30 mm. In the light of information given in figure 2, it is apparent that such a decrease will markedly alter the curve of dissociation of oxyhemoglobin, causing the hemoglobin to cling more tenaciously to its oxygen. In this manner the respiratory alkalosis precipitated by hyperventilation may bring about an actual impairment of release of oxygen from hemoglobin to the tissue of the body.

When a patient, by hyperventilation, has reduced the partial pressure of carbon dioxide in the serum from 45 to 15, he has brought about a condition wherein he has reduced by 61 per cent the amount of oxygen released in the tissues, if calculated at a value of 40 for the partial pressure of oxygen, or by 67 per cent if calculated at a value of 20 for the partial pressure of oxygen (table 1). The foregoing values are doubtless illustrative in a general way, of what takes place in man but are slightly inexact inasmuch as they are based on the behavior of hemoglobin derived from the horse, in which the hemoglobin is somewhat different from that of man. Barcroft's work on curves of dissociation of oxyhemoglobin is based on the behavior of hemoglobin derived from the horse. The hemoglobin of man, which has been studied less extensively than that of the horse, behaves in a manner similar to, but not identical with, that of the horse.[6] Furthermore, the foregoing values are somewhat inexact because of the fact that changes in the hydrogen ion concentration brought about within the erythrocyte may not parallel those in the plasma, although an equilibrium exists between intracellular and extracellular fluids.

Table 1
Example of effect of variable partial pressures of oxygen and carbon dioxide on the exchange of oxygen in the tissues

Oxygen, partial pressure, mm. of Hg	Carbon dioxide, partial pressure, mm. of Hg	Hemoglobin saturated with oxygen, per cent			Decreased O_2 to tissues because of acapnia, per cent
		Entering tissues	Leaving tissues	Difference	
40	45	95	72	23	61
	15	95	86	9	
20	45	82	34	48	67
	15	82	66	16	

6. Bock, A. V., Field, H., Jr. and Adair, G. S.: The oxygen and carbon dioxide dissociation curves of human blood. J. Biol. Chem. 59:353-378 (Mar.) 1924.

After hyperventilation the consumption of oxygen by the body is said to be decreased. Herxheimer and Kost[7] considered this to be a result of storage of oxygen, by an unknown mechanism, in the body during hyperventilation. Soley and Shock[8] have pointed out that this decreased utilization of oxygen is, in part, only apparent and not real and results from an increase in the partial pressure of oxygen in the alveoli which is brought about by hyperventilation. Such an increase in the tension of oxygen in the alveoli affects somewhat the results of analysis of the alveolar gases after hyperventilation.

It has been pointed out herein that an actual decrease in the amount of oxygen available in the tissues[9,10] may be a factor in the reduction in intake of oxygen by a subject after hyperventilation. This deficiency is augmented by the known decrease in transport of oxygen to the tissues which results from lessened blood flow to the tissues incident to lowering of the tension of carbon dioxide in the tissues. In turn, the size of vessels leading to anoxic tissue may become smaller as a result of lowered utilization of oxygen by the tissues.

There is, evidently, parallelism between the symptoms which result from hyperventilation and those which result from breathing rarefied air—so-called mountain sickness.

The known electrocardiographic change which occurs in normal and in diseased hearts after hyperventilation warrants further consideration in respect to its relationship to the lack of oxygen which is apparent in the tissues in the course of hyperventilation. Thompson[11] reported changes in the T wave of the electrocardiograms of normal subjects after hyperventilation. Barach and his associates[12] studied the effects of the anoxia test for coronary insufficiency to determine whether the effects of hyperventilation contributed to the electrocardiographic changes noted. They found that reduced pressure of oxygen sufficient to bring about a given degree of saturation of arterial blood would evoke less change in the electrocardiogram when carbon dioxide in small percentage was added to the gas inhaled than would a similar pressure of oxygen when carbon dioxide was not added to the gas inhaled. The electrocardiographic changes following hyperventilation were largely ascribed to anoxia which resulted from

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narrowing of blood vessels caused by the lowered pressure of carbon dioxide in the tissues, although the possibility that respiratory alkalosis might play a role had been suggested to Barach and his co-workers in a personal communication from Macleod. However, an effect just as important as that of anoxia which results from narrowing of blood vessels would appear to be that of impaired release of oxygen from hemoglobin to the myocardium which occurs with a decrease of carbon dioxide pressure.

Inadequately explained is the occurrence of extensive myocardial infarction particularly in approximately a half of the patients who sustain widespread lesions of myocardial necrosis in the absence of coronary thrombosis. It appears that a generalized, though transient, factor is effective in precipitating such a catastrophe. The occurrence of increased demand for oxygen by the myocardium during exertion associated with respiratory alkalosis may explain some such instances. While acapnia may occur after exertion, its effect on the curve of dissociation of oxyhemoglobin is largely offset by the accumulation of lactic acid.[13] However, the peculiarity of the myocardium in selectively utilizing lactic acid for nutrition may result in impairment of release of oxygen from hemoglobin in that tissue. Particularly should respiratory alkalosis be an etiologic factor in those who have relatively little disease of the coronary arteries and who sustain myocardial infarction following strenuous exertion to which they are unaccustomed.

The effect of hyperventilation on the central nervous system, especially with reference to the incidence of disorders characterized by convulsions, is striking. Lennox and his co-workers[14,15] showed that either decrease in content of oxygen of inspired air or hyperventilation will increase the tendency to convulsions. Conversely, it was shown that either acidosis or increase in degree of saturation of tissues with oxygen would lead to decrease in frequency of occurrence of such episodes. The effect of hyperventilation in accentuation of a tendency toward dysrhythmia, as evidenced by the occurrence of electro-encephalographic changes, is well known. These facts bear out the clinical observation that fatigue will at times increase the frequency of phenomena characterized by convulsions and that, especially in children, acidosis induced through dietary changes will decrease the frequency of occurrence of convulsions. It may well be that either hyperventilation or the acidosis induced by a ketogenic diet affects the frequency of occurrence of convulsions by their influence on the release of oxygen within the central nervous system.

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13. Lewis, Thomas, Ryffel, J. H., Wolf, C. G. L., Cotton, T. and Barcroft, Joseph: Observations relating to dyspnoea in cardiac and renal patients. Heart 5:45-92 (Oct. 14) 1913.
14. Lennox, W. G. and Behnke, A. R., Jr.: Effect of increased oxygen pressure on the seizures of epilepsy. Arch. Neurol. & Psychiat. 35:782-788 (Apr.) 1936.
15. Lennox, W. G. and Cobb, Stanley: Epilepsy from standpoint of physiology and treatment. Medicine 7:105-290 (May) 1928.

As yet knowledge concerning chemical changes which take place in the functioning tissues of the body is inadequate. Certainly quantitative values presented herein and arrived at by indirect observation portray only the tendency of the reactions which occur in the cell. These data represent at best but approximations of such changes which occur in the course of cellular respiration. However, it may be concluded that an important factor in the causation of symptoms by respiratory alkalosis is the effect that such alkalosis has on intracellular exchange of gases.

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CHRONIC RELAPSING PANCREATITIS; A REVIEW OF CASES IN WHICH DISEASE OF THE BILIARY OR GASTRO-INTESTINAL TRACT DID NOT COEXIST

Earl E. Gambill, M. D., M. S. in Medicine, Division of Medicine:

Chronic relapsing pancreatitis characteristically is a disease of recurring, acute, painful exacerbations separated by variable intervals of relative clinical quiescence. Early in the disease, function of the islet and acinar cells is disturbed only at the time of the attacks; eventually the disturbances become permanent and chronic and result in steatorrhea, creatorrhea and diabetes mellitus. Pancreatic calcification, formation of pseudocysts and other complications may develop. The disease tends to be progressive, the attacks becoming more frequent, more prolonged and more severe. The clinical picture is due not only to disease in the pancreas but also to the effects of the disease on neighboring organs.

Chronic relapsing pancreatitis apparently is a relatively uncommon disease. In a recent five year study it was found that about

twenty cases were encountered each year at the Clinic. The incidence has increased since physicians have become more familiar with the disease. I think that the incidence is greater than the figures indicate.

The youngest age at which the attacks began in the twenty-nine cases under consideration was ten years; the oldest, sixty-six and the median, thirty-seven years. In 48 per cent of cases the attacks began before the patients were thirty years of age. The sex ratio in this series was six males to one female. Patients were not obese, for the average weight at the onset of the disease was only 5 pounds (2.3 kg.) more than the standard.

Alcohol was used by two thirds of the patients, heavily by a third. It appeared to be a provocative factor in the acute episodes of 14 per cent of those patients who used alcohol.

An acute attack of severe pain was the first sign of the disease in fourteen of the twenty-nine cases. In five of these fourteen cases the early episodes of pain were relatively mild. In others dyspepsia of the flatulent type preceded the first attack of pain by one to several years. It is not certain whether such dyspepsia is due to, or independent of, pancreatic disease. Sooner or later the milder manifestations are followed by an acute, severe, prolonged attack of pain, dispelling any doubt that organic disease has appeared.

The acute manifestations tend to recur for a period of years, in this series for as long as nineteen years, the average history being 5.7 years. The most characteristic feature of the acute attack is its prolonged duration, as illustrated in table 1. Unlike uncomplicated biliary colic, one injection of morphine usually does not terminate the attacks of pancreatitis. These attacks seldom last less than two days and often last for from two to fourteen days, sometimes longer. The more prolonged ones tend to occur later in the disease.

Pain in the acute episodes may be sudden in onset and termination but often it begins mildly, gradually increases in severity until a plateau is reached, and then gradually subsides in a period of hours or days. The pain of pancreatitis tends to be steady rather than colicky, although waves of accentuation may be superimposed on the steady pain, which was described variously as burning, sharp, stabbing, cramping, pressing or aching.

The primary site of the pain may be in the right, middle or left part of the epigastrium, or rarely in the lower thoracic portion of the back. From the primary site, pain may be propagated to various parts of the abdomen, thorax and thoracolumbar region of the back. Pain starting in, or shifting to, the left upper part of the abdomen and left side of the back is the most suggestive site for pancreatitis.

During an attack of pancreatitis the patient is often restless, perspires freely, has a tense, distended abdomen and may be found sitting with the trunk flexed forward, since that position may afford

some relief. Emesis, diarrhea, intestinal rumbling, fever, chills, jaundice, tachycardia or tenderness and spasm in the upper portion of the abdomen may be associated with the other symptoms, and at times an enlarged pancreas or pancreatic cyst may be palpated. Tenderness in the upper portion of the abdomen, especially on the left, may be noted for days after cessation of pain. Subclinical or clinical icterus was present in ten cases. Leukocyte count, sedimentation rate and Quick prothrombin time may or may not be increased during the acute seizures.

Table 1

Duration of seizures of pain in twenty-nine cases of chronic relapsing pancreatitis

Duration of pain	Cases
Less than 1 hour	1
1 - 5 hours	2
6 - 11 hours	1
12 - 23 hours	1
2 - 6 days	6
7 - 13 days	7
14 - 20 days	1
21 - 27 days	2
28 - 35 days	6
Not determined	2

In about one half of the cases recently studied by Drs. Comfort, Baggenstoss and me, the acute painful exacerbations of the disease were followed by certain permanent sequelae, including diabetes, steatorrhea and calcification, that are recognizable in the interval between the attacks and are diagnostic in character. In the other half of the cases (and it is this half that I want to discuss more fully), in the interval between attacks the clinician was unable to demonstrate pancreatitis by physical or laboratory methods of examination; yet the surgeon and the pathologist were able to demonstrate the characteristic pathologic changes. However, in this group of cases in which destruction of the pancreas has not progressed to the stage of permanent sequelae, the clinician may demonstrate during the acute painful exacerbation of the disease transitory disturbances of pancreatic function—that is, transitory increases in values for amylase and lipase in the serum and transitory glycosuria and hyperglycemia which disappear as the exacerbation subsides. If the patient is seen during an acute exacerbation, the diagnosis may be made certain by demonstration of these transitory disturbances of pancreatic function.

On the other hand, if the patient is seen in the interval between the attacks, a tentative diagnosis of relapsing pancreatitis may be made only after exclusion of other causes of upper abdominal pain and on the basis of recurring episodes of acute upper abdominal pain. It is in these cases that in the absence of diagnostic disturbances of pancreatic function an accurate description of the painful episode, including the type of onset and conclusion of the attack, the character of the pain, its location, radiation and duration, is of greatest value in making a presumptive diagnosis of recurrent pancreatitis.

Some of the foregoing points are illustrated by the following case.

REPORT OF CASE

A white man, aged thirty-nine years, first registered at the Clinic September 4, 1934. He used alcohol heavily, worked hard and ate heartily. In August, 1934, he had suffered for a few days from a pain high in the epigastrium and loose stools, and then on August 17 became acutely ill. The pain became very severe, spreading through to the back and to the anterior portion of the thorax. It was aggravated by breathing and accompanied by nausea, vomiting and bloating. The systolic blood pressure dropped to 86 mm. of mercury. His maximal temperature was 101.5° F. The leukocyte count went as high as 19,000 per cubic centimeter of blood. There were slight icterus, marked abdominal tenderness and some rigidity. The patient had had two similar attacks in the preceding six months.

Physical examination at the Clinic disclosed mild jaundice, epigastric tenderness and rigidity. The temperature was 101.5° F. The concentration of bilirubin was 1.2 mg. per 100 c.c. of serum and the van den Bergh reaction was direct. The sedimentation rate was slightly elevated. Urinalysis, blood counts and a routine serologic test for syphilis gave negative results. Roentgenograms of the gallbladder (Graham-Cole technic) and stomach were normal. Urinary diastase was less than 150 units. The diagnosis was acute pancreatitis.

The patient returned in 1935, 1936, 1937 and 1938. Five attacks of pain occurred in these years. The physical and laboratory investigations always gave normal results. Roentgenologic examination of the gallbladder in 1935 and 1937 revealed a normally functioning organ. In February, 1939, a severe attack was followed by jaundice, which persisted for three weeks. On March 27, 1939, physical examination and laboratory tests gave negative results except that the concentration of bilirubin was 1.3 mg. per 100 c.c. of serum and the van den Bergh reaction was direct. The diagnosis was chronic pancreatitis.

An exploration carried out March 28 revealed a thick-walled edematous gallbladder without stones. The moderately dilated common bile duct did not contain stones. The liver was purplish. The pancreas was hard throughout, more so in its head than in its other

portions. Probes were passed through the ampulla with difficulty. A T tube was placed in the common duct and cholecystostomy was done. The T tube came out spontaneously six weeks after operation.

Severe attacks recurred in August, 1940, December, 1942, and April, 1943. These were characterized by nausea, vomiting, constipation, fever and leukocytosis lasting four to ten days. In April, 1943, urinalysis and blood count gave negative results. A cholecystogram revealed a normally functioning gallbladder. The concentrations of serum amylase, lipase and bilirubin were normal. The last attack occurred several weeks before the patient's final admission in June, 1944. At this time there was no demonstrable disturbance of pancreatic function. Death occurred in July, 1944, following left pneumonectomy for carcinoma of the left lung.

At necropsy the gallbladder appeared normal grossly but the bile ducts were found to be moderately dilated. The pancreas was estimated to weigh almost 70 gm. and the consistency was markedly increased. The cut surface revealed broad bands of fibrous connective tissue, which separated islands of parenchyma. In the head and body of the pancreas there were several irregularly dilated spaces, some of which contained a pale, yellowish green, semisolid material. They were interpreted as evidence of previous necrosis and enzymatic digestion of the parenchyma. Histologic study of the pancreas revealed severe interlobular and mild intralobular fibrosis. Moderate numbers of lymphocytes, some with a perineural distribution, were present. Sections of the gallbladder revealed foci of lymphocytes in the mucosa and muscularis.

COMMENT

Emphasis may be placed on the following points in the preceding report of a case. First, in spite of the repeated attacks of pancreatitis over a period of ten years, pancreatic calcification, diabetes and steatorrhea did not occur. Values for blood sugar and for amylase and lipase in the serum were normal in the interval between the attacks. There was neither steatorrhea, diabetes, calcification nor transitory disturbances of pancreatic function on which to base the diagnosis of relapsing pancreatitis. Second, the painful exacerbations were of several days' duration. One attack lasted three weeks. Attacks of such severity due to cholecystic disease should be associated with roentgenologic evidence of cholecystic disease. By exclusion of other diseases and because of the definitely organic nature of the attacks, their severity and duration, a presumptive diagnosis of chronic relapsing pancreatitis was made. Third, the pathologic findings, as illustrated in figure 1*a* in Dr. Baggenstoss' paper leave no doubt that the pancreas was extensively and permanently diseased even though permanent disturbances of function were not demonstrated

clinically. Fourth, transitory jaundice and the subsequent disappearance of the edema and thickening of the gallbladder which had been observed at operation in March, 1939, point to the transitory nature of the involvement of the biliary tract in this case.

Chronic pancreatitis, then, usually is a relapsing, painful, progressive disorder which affects any age group and is more common in males than in females. Early in the disease, disturbances of pancreatic function may be demonstrated only during the acute exacerbations; eventually, owing to progressive destruction of the pancreas, its function becomes chronically and permanently deficient. Until destruction of the pancreas becomes extensive enough to produce diabetes mellitus, steatorrhea, pseudocysts large enough to be palpable and calcification, the history of recurring seizures of pain may be the sole evidence available to the clinician for the presumptive diagnosis of chronic relapsing pancreatitis when the patient is studied in the intervals between the acute exacerbations.

CHRONIC RELAPSING PANCREATITIS: A REVIEW OF THE PATHOLOGIC ANATOMY IN CASES IN WHICH DISEASE OF THE BILIARY OR GASTROINTESTINAL TRACT DID NOT COEXIST

Archie H. Baggenstoss, M. D., M. S. in Pathology, Section on Pathologic Anatomy: Grossly the pancreas in cases of chronic relapsing pancreatitis is indurated and sometimes nodular. Atrophy was apparent in some instances although in one case the gland was larger than normal. Infiltration with fat was extensive in one case. The cut surface revealed broad bands and masses of fibrous connective tissue which separated the parenchyma into irregular islands. Pseudocysts were found in four cases (fig. 1*a*). They varied in size from 1.0 cm. to 20.0 cm. in greatest diameter. The contents of these pseudocysts varied from cloudy, colorless fluid to yellowish green, semisolid, necrotic material. The walls were composed of dense fibrous connective tissue. In one case there was a cavity in the head of the pancreas 7.0 cm. in diameter lined by necrotic material and fibrinopurulent exudate. The cavity communicated with the first portion of the duodenum by a fistula. It was interpreted as an old abscess, the residual of previous acute hemorrhagic pancreatitis, which had perforated secondarily into the duodenum and thus had drained spontaneously (fig. 1*b*). Macroscopic calcification in the pancreas was observed in three cases and so-called fat necrosis in the adipose connective tissue adjacent to the pancreas was found in two cases. The common bile duct revealed varying degrees of dilatation in five cases,

while the gallbladder was dilated in four cases. Mild chronic cholecystitis was present in one case.

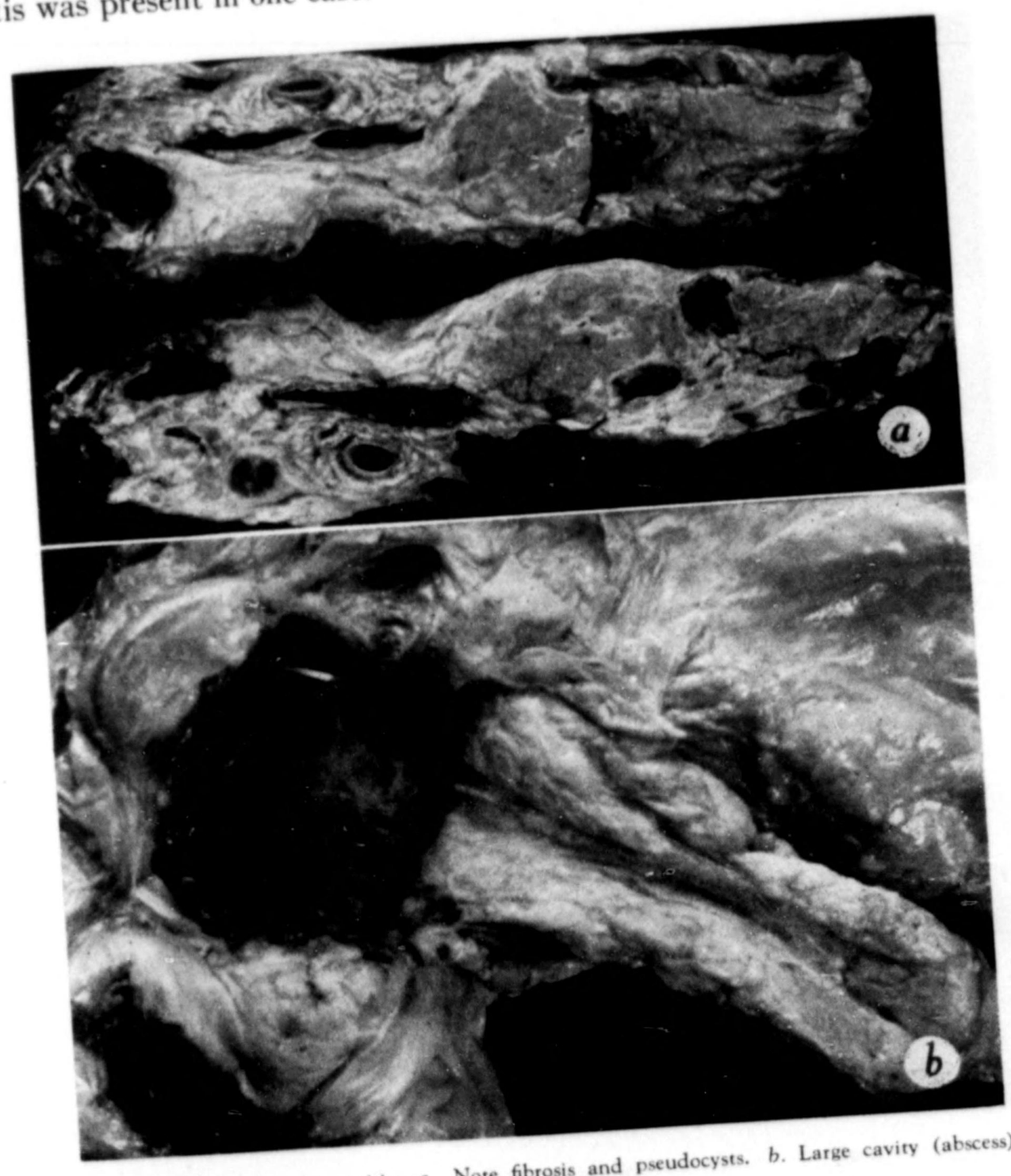

Fig. 1. Chronic pancreatitis. *a*. Note fibrosis and pseudocysts. *b*. Large cavity (abscess) in head of pancreas. Probe indicates site of fistula into duodenum.

HISTOLOGIC EXAMINATION

Fibroblastic proliferation and fibrosis were prominent features of all sections of the pancreas examined. Interlobular fibrosis was more pronounced than intralobular or interacinar fibrosis (fig. 2*a*). Interlobular fibrosis was mild in two cases, moderate in four cases. Intralobular fibrosis was mild in four cases and moderate in two cases. In four cases the biopsy revealed no lobular arrangement but only masses of fibrous connective tissue. In one case the interstitial

us (fig. 2*b*). The acini were
d. Frequently they appeared as
ormal arrangement around a central

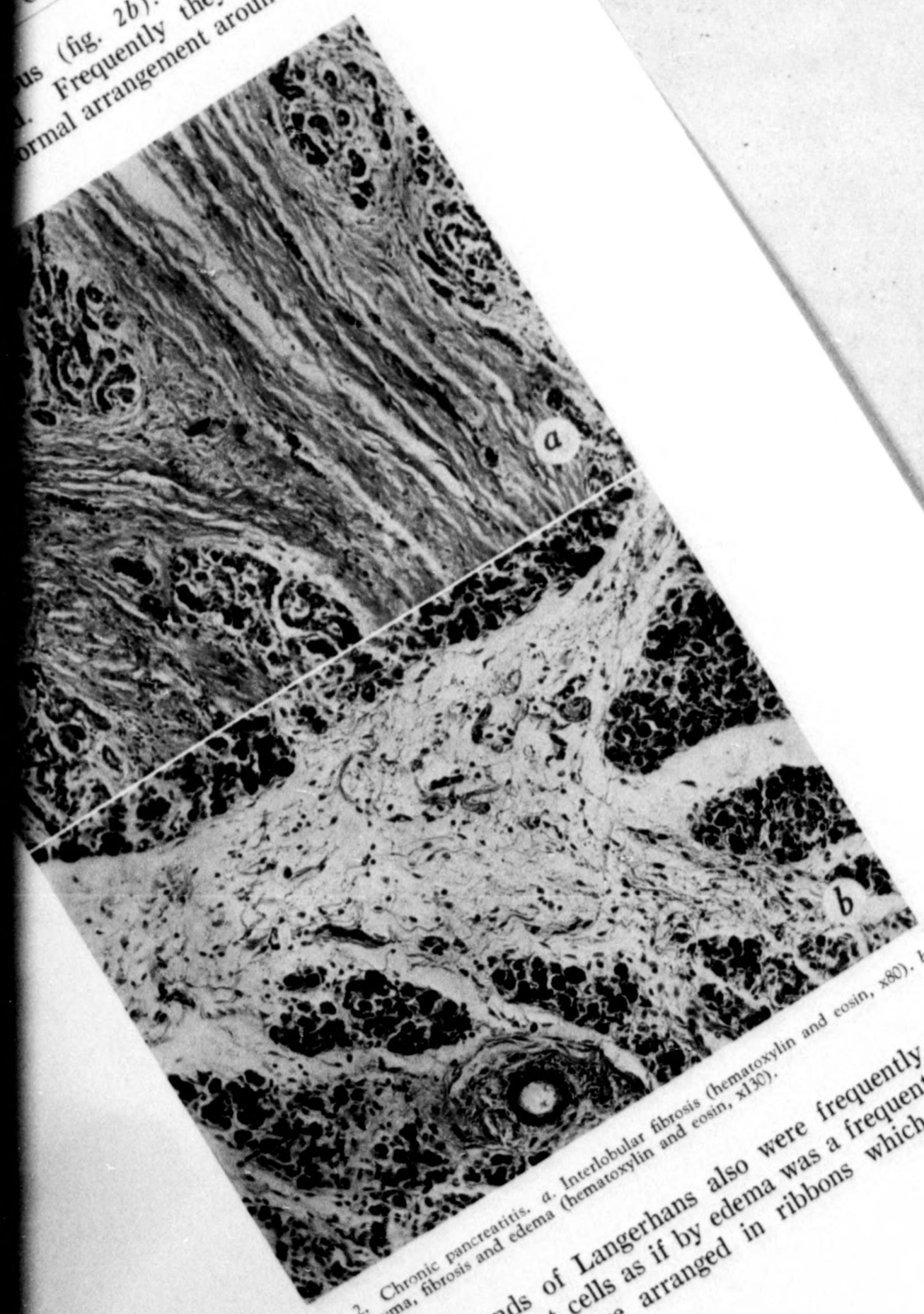

Fig. 2. Chronic pancreatitis. *a*. Interlobular fibrosis (hematoxylin and eosin, x80). *b*. Atrophy of the parenchyma, fibrosis and edema (hematoxylin and eosin, x130).

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Separation of the islet cells as if by edema w
Sometimes the cells were arranged in ribbons

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connective tissue appeared edematous (fig. 2*b*). The acini were usually artophied and disorganized. Frequently they appeared as small groups of cells without the normal arrangement around a central

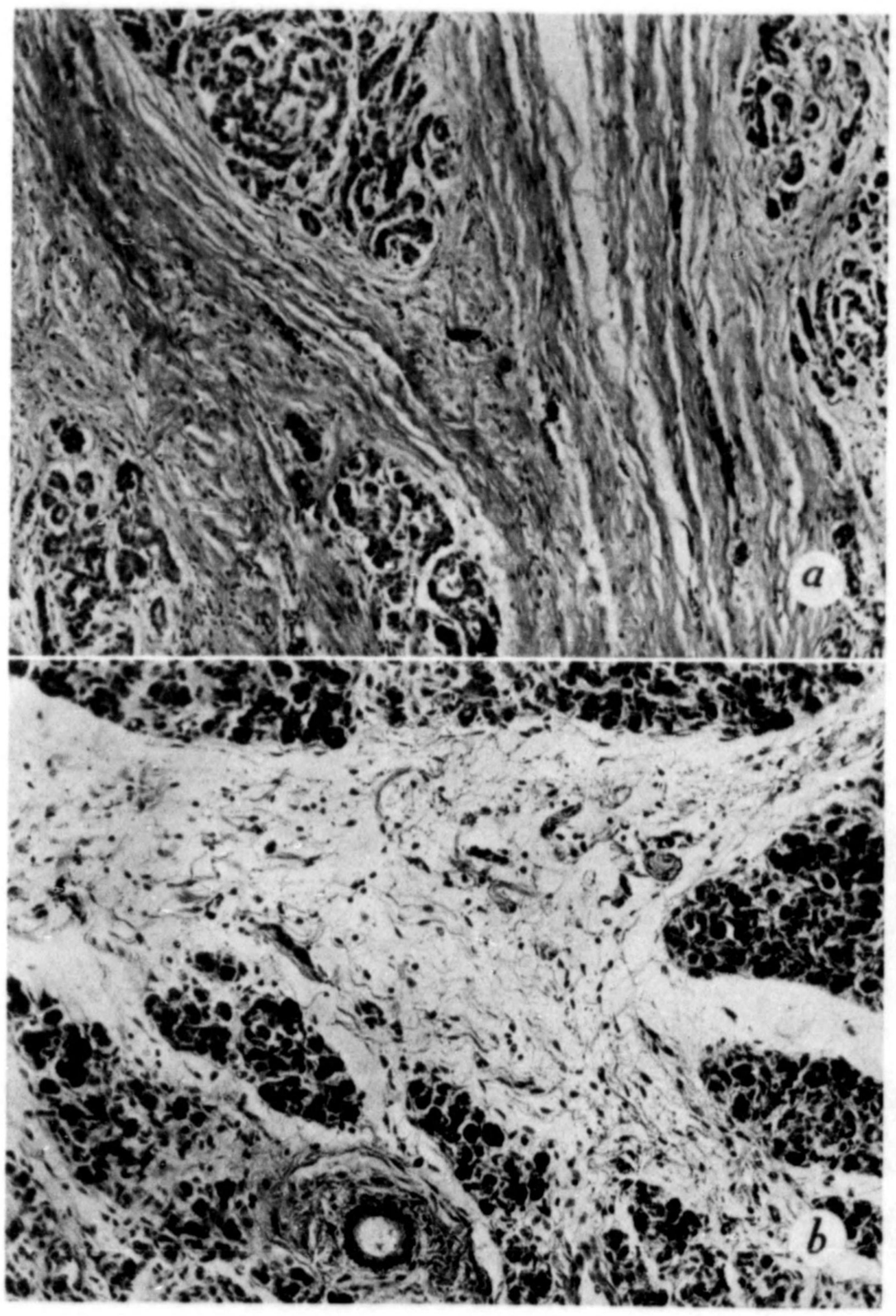

Fig. 2. Chronic pancreatitis. *a*. Interlobular fibrosis (hematoxylin and eosin, x80). *b*. Atrophy of the parenchyma, fibrosis and edema (hematoxylin and eosin, x130).

lumen. The islands of Langerhans also were frequently atrophied. Separation of the islet cells as if by edema was a frequent occurrence. Sometimes the cells were arranged in ribbons which were widely

separated. Occasionally cellular and hypertrophied islets in which the cells contained giant nuclei were observed. These changes were interpreted as indicating compensatory hyperplasia.

Lymphocytes and plasma cells were present in moderate numbers in all cases. They were found diffusely distributed throughout the regions of fibrosis and also in focal collections. In four cases a perineural distribution of lymphocytes was prominent (fig. *3a*). Eosinophilic leukocytes were present in the interstitial connective tissue in moderate numbers in three cases. Actual suppuration was observed in only one case. This occurred in the wall of a resolving abscess which had perforated and drained spontaneously into the duodenum. Foreign body giant cells were present in three cases. They were usually found in association with cholesterol crystal clefts (fig. *3b*). Hemosiderin deposits were observed in five cases while calcium deposits in the interstitial connective tissue were observed in three cases.

There was histologic evidence of slight to moderate dilatation of the ducts in four cases. Laminated material, probably inspissated mucus, was present in two cases. So-called squamous metaplasia or squamatization of the epithelium of the ducts occurred in one case (fig. *3c*).

Arteriosclerosis was pronounced in some cases. The most prominent change was a proliferation of connective tissue cells which had led to thickening of the intima and narrowing of the lumen. Arteriosclerosis was absent or of mild degree in three cases, moderate in two and severe in four cases.

COMMENT

In summarizing the anatomic and histopathologic features of chronic pancreatitis one is particularly impressed by two rather constant findings—interstitial fibrosis and residual necrosis of tissue. The former was present in all cases. Interlobular fibrosis was more pronounced than intralobular fibrosis and both were associated with extensive atrophy of the parenchyma. Whether this represents a continuing chronic inflammatory process or the regressive and end phase of repeated attacks of acute inflammation is difficult to say from the histologic appearance alone. When the histologic features are studied in the light of the known clinical facts regarding the course of the disease it seems likely that the latter interpretation is the correct one for most of the cases.

In those cases in which one can exclude the presence of regions of necrosis in the entire pancreas (fig. *2b*) it would seem logical to attribute the interstitial fibrosis and atrophy of the parenchyma to repeated attacks of acute interstitial inflammation of the type described by Elman.

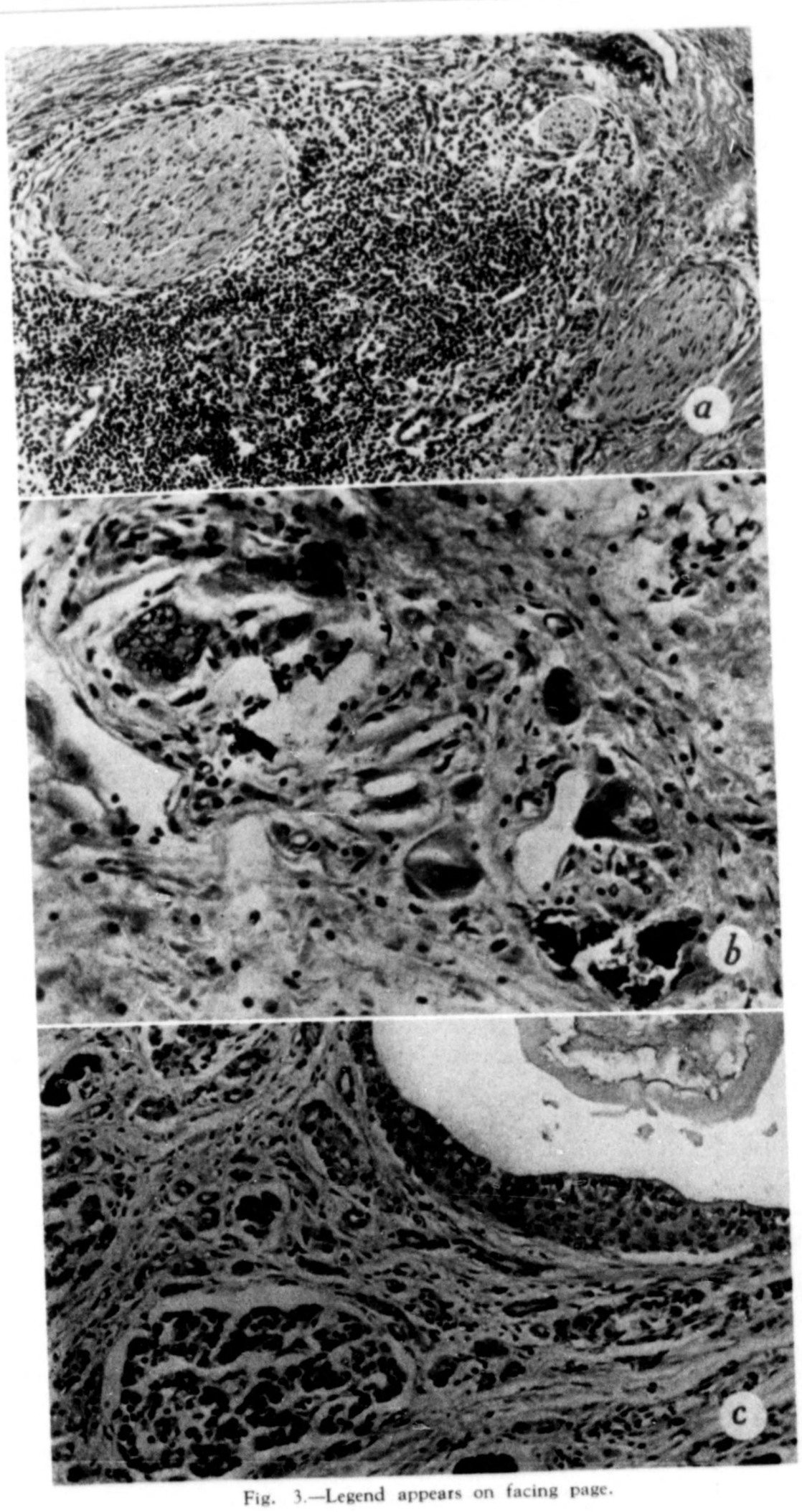

Fig. 3.—Legend appears on facing page.

In those cases in which necrosis of tissue occurred, the inflammatory process probably was closely related to so-called acute hemorrhagic pancreatitis. In other words, we were probably dealing with repeated sublethal attacks of acute hemorrhagic pancreatitis with necrosis. For reasons at the present time not well understood, the inflammatory and necrotizing process in these cases subsided and allowed time for fibrosis and atrophy to occur. In this connection it may be said that the pseudocysts which were found in these cases were interpreted as the result of acute inflammation, necrosis of tissue and the subsequent digestive action of liberated pancreatic enzymes. Whether obstruction of pancreatic ducts played a role in the production of pseudocysts is problematic.

The perineural distribution of lymphocytes which was observed in four cases is interesting in view of the fact that abdominal pain is such a prominent feature in these cases. Perhaps actual involvement of the nerves in the inflammatory process is responsible for the intense pain from which these patients suffer. The fact that moderate to severe arteriosclerosis was present in six of the ten cases in which tissue was available for study is interesting also in view of the fact that some workers attribute an important etiologic role to vascular occlusion in cases of acute pancreatic necrosis and hemorrhagic pancreatitis. In our cases, however, the arterial changes were interpreted as a result rather than as a cause of the pancreatic lesion. In our opinion the thickening of the arterial walls was probably the result of disuse and represented changes similar to those which occur in the senile uterus.

In summary therefore chronic relapsing pancreatitis may represent the summation of repeated attacks of acute interstitial pancreatitis or repeated sublethal attacks of so-called acute hemorrhagic pancreatitis, or perhaps in some cases a combination of the two types of pancreatitis.

Fig. 3. Chronic pancreatitis. *a*. Note perineural distribution of lymphocytes (hematoxylin and eosin, x105). *b*. Cholesterol crystal clefts, giant cells and deposits of calcium (hematoxylin and eosin, x215). *c*. Separation of islet cells as if by edema. Note squamatization of epithelium of duct (hematoxylin and eosin, x135).

CHRONIC RELAPSING PANCREATITIS; ITS CLINICAL COURSE, SEQUELAE, DIAGNOSIS AND MEDICAL TREATMENT IN CASES IN WHICH DISEASE OF THE BILIARY OR GASTRO-INTESTINAL TRACT DID NOT COEXIST

Mandred W. Comfort, M. D., M. S. in Neurology, Division of Medicine: As a participant in this symposium on chronic relapsing pancreatitis, I shall discuss the sequelae of chronic damage to the pancreas, emphasize the progressive character of the disease, and remark on its diagnosis and medical treatment.

In less than half of the twenty-nine cases of the series recently made the subject of study by Drs. Gambill, Baggenstoss and me, acute painful exacerbations recurring over a period of one to ten years produced evidences of damage to the pancreas only during the acute exacerbations. As Dr. Gambill has pointed out these evidences of damage to and dysfunction of the pancreas consist of transitory elevation of values for enzymes in the serum and transitory glycosuria and hyperglycemia. In these cases in the interval between attacks, the existence of damage to the pancreas was not demonstrated clinically; yet fibrosis, atrophy and residual necrosis were the pathologic findings noted by Dr. Baggenstoss in sections removed for biopsy or at necropsy. Apparently extensive damage to the pancreas must occur before disturbances of function can be demonstrated clinically in the intervals between attacks.

In the remaining cases, destruction of the pancreas had progressed farther than in the first group of cases and existence of damage to the pancreas in the intervals between attacks was proved clinically by demonstration of one or more of the following: diminution of secretion of enzymes, bicarbonate and volume of the pancreatic juice; excess of fat and of nitrogen in the feces; diabetes; deposition of calcium in the pancreas, or formation of pseudocysts.

In the following case, the appearance in turn of diabetes, calcification and steatorrhea following repeated exacerbations illustrates the progressive destruction of the pancreas so characteristic of the disease.

REPORT OF CASE

A man first seen at the Clinic at the age of thirty-six years stated that his first attack of upper abdominal pain had occurred four years previously at the age of thirty-two years. Thereafter attacks occurred every one to two months, lasting two to three days. At the age of thirty-five years, following an unusually severe attack lasting one week, diabetes was discovered. The attacks became more frequent

and on examination at the age of thirty-six years the secretin test disclosed great impairment of external pancreatic secretion but not enough to produce steatorrhea. Deposition of calcium in the pancreas was demonstrated roentgenologically and the existence of diabetes was confirmed. At operation an enlarged, hard pancreas was found and cholecystogastrostomy was performed. The painful seizures temporarily ceased. One year later, at the age of thirty-seven years, the pain reappeared and became almost continuous. Vomiting and diarrhea with gross steatorrhea appeared. On examination it was found that a total of 60 pounds (27.2 kg.) had been lost and that emaciation was marked. There was vomiting of the retention type and on roentgenologic examination gastric dilatation was demonstrated. Incapacitation was complete, and morphinism had become a problem.

At operation, the markedly enlarged, hard pancreas, gastric dilatation, and obstruction of the superior mesenteric vein with formation of many varicosities were noted. Posterior gastro-enterostomy was performed. With relief of obstructive symptoms a high caloric, low fat diet, together with fifteen enteric-coated pancreatin tablets (each 5 grains [0.3 gm.]) with each meal, improved the state of nutrition, reduced abdominal discomfort and controlled the diarrhea. Painful seizures continued to occur but have been less serious.

CLINICAL DATA

This case illustrates not only the progressive destruction of the pancreas and the appearance in turn of several sequelae, but also the frequently seen progressive increase in severity and duration of the painful attacks. In other cases, the destruction proceeds more slowly than in this case and many years may elapse between the first painful attack and the appearance of clinical evidence of chronic damage.

Deposition of calcium was demonstrated roentgenologically in thirteen of the twenty-nine cases (45 per cent). It was demonstrated as early as the *first* and as late as the *nineteenth* year after the initial attack. Calcium is deposited as areas of calcification in the parenchyma or as stones in the ducts. The deposit of calcium may be localized or it may be widespread throughout the organ to such a degree that the pancreas is clearly outlined in the roentgenograms. I believe that stones in the duct usually are the result, not the cause, of the pancreatitis. The belief that this is so is supported by cases seen in increasing numbers in which calcification appeared while the patients were under observation. Thus, in the case in which roentgenograms reproduced in figure 1 were taken, deposition of calcium was not demonstrable during the fourteenth year but was demonstrated in the nineteenth year of the disease. Diabetes developed three years later. Gross steatorrhea had not appeared at the time of writing, twenty-five years after onset.

Diabetes developed in seven of the twenty-nine cases (24 per cent). It appeared as early as two years and as late as twenty-three years after the initial attack. It often appeared following an especially severe attack. The diabetes usually is mild but may be severe. The retinopathy and peripheral neuritis of diabetes have been observed.

Gross steatorrhea appeared in eight of the twenty-nine cases (28 per cent). Steatorrhea is accompanied by azotorrhea. The daily loss of fat and nitrogen in the feces rarely attains that seen in complete external pancreatic insufficiency due to total pancreatectomy.

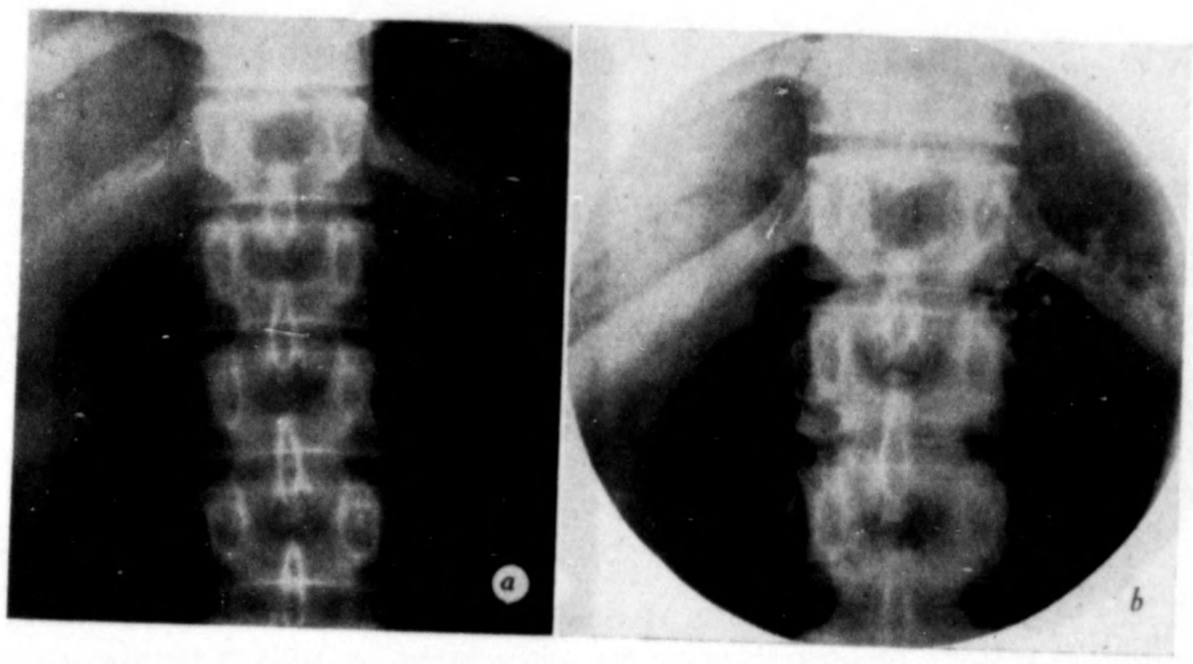

Fig. 1. Chronic relapsing pancreatitis. *a*. Fourteen years after the first attack. Note absence of evidence of deposition of calcium. *b*. Nineteen years after the first attack. Calcium is now visible.

Pseudocysts developed in four cases (14 per cent). Usually they developed following severe, prolonged attacks during which destruction of an area of the pancreas by hemorrhagic necrosis later resulted in cyst formation.

Sequelae other than those arising from destruction of the pancreas complete the clinical picture of chronic relapsing pancreatitis. The enlarged pancreas may press on and obstruct the duodenum with retention vomiting, which probably took place in the case reported in this paper. It may partially obstruct the common bile duct with secondary dilatation of the common bile duct and gallbladder and transitory or chronic jaundice. It may press on and obstruct the superior mesenteric veins with formation of varicosities, as in the case reported in this paper.

Pancreatitis may involve the gastro-intestinal tract. There may be duodenitis and gastritis, gross gastro-intestinal hemorrhage, disturbed motility with prolonged retention of barium and food in the

stomach, slowed motility of the bowel with symptoms suggesting obstruction, and diarrhea.

Among common miscellaneous sequelae are loss of weight and malnutrition. Frank vitamin deficiency states, hypoproteinemia with nutritional edema, and hypolipemia are rare. Hypocalcemia with tetany is very rare and my colleagues and I have not encountered osteoporosis. Hypoprothrombinemia is relatively frequent but this has occurred only with jaundice. Anemia is common and hypochromic in type. Macrocytosis has been seen only in cases with jaundice and hepatitis.

TERMINAL ASPECTS

The acute, painful attacks may diminish in severity and frequency. Rarely, they may cease completely before or after extensive damage to the pancreas. The disease may progress to development of all sequelae, including emaciation, morphinism and complete disability. Death may be due to the disease of the pancreas itself, that is, to acute hemorrhagic necrosis, gross gastro-intestinal hemorrhage, pylephlebitis or abscess of the pancreas. More often, death is due to unrelated diseases such as carcinoma, cerebral vascular accidents or intercurrent infections.

DIAGNOSIS

The diagnosis of chronic relapsing pancreatitis without associated disease of the gastro-intestinal or biliary tract should be made in a high percentage of cases. *When disease of neighboring organs has been excluded by appropriate tests,* chronic relapsing pancreatitis is suspected because of a history of repeated attacks of abdominal (usually epigastric) pain, especially when the pain has been severe, of more than one or two days' duration or located in the left epigastric region and when a mass can be felt in the region of the pancreas. Existence of disease of the pancreas in such cases can be proved during the painful attack by demonstration of transitory elevation of values for enzymes in the serum and by transitory glycosuria and hyperglycemia, and can be proved both during the acute attacks and in the interval between the acute attacks by demonstration of frank diabetes, of steatorrhea, and of deposits of calcium in the pancreas. When the patient is seen in the interval between the attacks and these diagnostic sequelae of pancreatitis have not developed, a presumptive diagnosis may be made on the basis of those characteristic features of the acute exacerbation described by Dr. Gambill.

TREATMENT

During the acute attack, opiates, intravenous administration of fluids, decompression of the gastro-intestinal tract and accepted measures for combating shock are used as indicated.

During the chronic phases, alcohol is forbidden, diabetes is controlled, external pancreatic insufficiency and the resulting steatorrhea and azotorrhea are treated by a high caloric, high protein, high carbohydrate, low fat diet, by substitution therapy in the form of enteric-coated pancreatin tablets or by both measures. Fifteen grams of pancreatin daily will reduce the loss of food as much as 50 per cent.

Surgical treatment alone appears to offer prolonged relief from the painful attacks and such relief occurs in only about 50 per cent of the cases in which surgical treatment is used.

CONCLUSIONS

Chronic relapsing pancreatitis characteristically is a disease of recurring painful exacerbations separated by long or short periods of relative clinical quiescence. During the early stages of the disease the clinician may not be able to demonstrate existence of pathologic physiologic changes by physical or laboratory methods of examination in the interval between attacks; yet the surgeon or the pathologist will be able to demonstrate pathologic changes in the organ. However, later in the course of the disease the destruction of the pancreas will reach the point where disturbances of internal and external secretion, pancreatic calcification and other sequelae will be demonstrable at all times. Diagnosis should be made with a high degree of accuracy. Medical measures adequately control the pathologic physiologic disturbances but do not appear to affect the course of the disease.

Surgical treatment alone appears to offer relief from disabling pain.

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DIABETES MELLITUS ASSOCIATED WITH CHRONIC RELAPSING PANCREATITIS

Randall G. Sprague, M. D., Ph. D. in Medicine, Division of Medicine: In 1788, an English physician, Thomas Cawley,[1] described the case of a man, "aged thirty-four years, strong, healthy and corpulent, accustomed to free living and strong corporeal exertions in the pursuit of country amusements," who, "in December, 1787, was seized with diabetes; . . ." He gradually became emaciated and debilitated, and his urine was found to be sweet and to contain a substance which was fermentable with yeast. After treatment with a "variety of medicines, the usual consequence of inefficacy and despair," the patient died. A necropsy was performed: "The pancreas was full of calculi, which were firmly impacted in its substance. They were of various sizes, not exceeding that of a pea, white, and made up of a number of lesser ones, which made their surface rough, like mulberry stones; and in all respects they appeared analogous to the calculi which we sometimes meet with in the salivary ducts. The right extremity of the pancreas was very hard, and appeared to be scirrhous."

Cawley thought that the diabetes in this case was due to a disorder of the kidneys, and that the condition observed in the pancreas was a complication rather than the cause of the diabetes. Despite this misinterpretation of the facts, his case was the first reported in medical literature in which diabetes was recognized during life and a lesion of the pancreas was found at necropsy. It also was one of the earliest recorded descriptions of a case of chronic pancreatitis with pancreatic calculi. It was not until 101 years later, in 1889, that Minkowski,[2] with the aid of von Mering, performed pancreatectomy on a dog and thereby established experimentally a direct relationship of the pancreas to diabetes.

Chronic pancreatitis is also of historical interest in connection with the discovery of insulin. The classic experiments of Banting and Best[3] on ligation of the pancreatic ducts which led to the discovery of insulin were formulated in 1920 while Banting was reading a publication by Barron,[4] of the medical school of the University of Minnesota, dealing with the pathologic changes in the islet and acinar tissue of the pancreas in cases of pancreatic lithiasis. Barron

1. Cawley, Thomas: A singular case of diabetes, consisting entirely in the quality of the urine; with an inquiry into the different theories of that disease. London Med. J. 9:286-308, 1788.
2. Minkowski, Oscar: De l'extirpation du pancréas chez les animaux et due diabète expérimental. Semaine méd. 9:175, 1889.
3. Banting, F. G. and Best, C. H.: The internal secretion of the pancreas. J. Lab. & Clin. Med. 7:251-266 (Feb.) 1922.
4. Barron, Moses: The relation of the islets of Langerhans to diabetes with special reference to cases of pancreatic lithiasis. Surg. Gynec. & Obst. 31:437-448 (Nov.) 1920.

showed, among other things, that patients having pancreatic lithiasis who presented symptoms of hyperglycemia and glycosuria during life revealed definite lesions of the islets at necropsy.

It has been estimated that approximately 90 per cent or more of the islet tissue of the pancreas must be destroyed or removed before diabetes will become apparent. One would, therefore, logically expect that permanent diabetes would occur only in those cases of chronic relapsing pancreatitis in which the process was very severe or of very long duration, with resulting extensive damage to the islet tissue. Thus, in the series of twenty-nine cases of chronic relapsing pancreatitis without associated disease of the biliary tract studied by Comfort, Gambill and Baggenstoss, diabetes was present in eight cases, or about 28 per cent. No doubt diabetes will develop in many of the remaining cases if the patients survive sufficiently long and continue to have attacks of pancreatitis.

Table 1

Time elapsing between onset of symptoms of chronic relapsing pancreatitis and diagnosis of diabetes mellitus

Years	Cases
Less than 1	5
1 to 5	4
6 to 10	6
11 to 15	3
16 to 20	2
More than 20	4
Total	24

The remarks which follow are based on a study of twenty-four cases of diabetes associated with chronic relapsing pancreatitis seen in the Clinic from 1939 to 1945, inclusive. In all of these cases the pancreatitis was severe enough to account for the presence of diabetes, although a family history of diabetes in seven of the cases suggests that heredity, as well as the destructive process in the pancreas, might have been an etiologic factor. These twenty-four cases make up approximately 0.3 per cent of all the cases of diabetes mellitus seen in the Clinic during this period, a fact which serves to emphasize that pancreatitis is an infrequent cause of diabetes.

In the majority of the twenty-four cases, diabetes became apparent only after a series of exacerbations of the pancreatitis over a period of several years. In fifteen cases the symptoms of pancreatitis preceded the discovery of diabetes by more than five years (table 1). The five cases in which less than a year elapsed between

the onset of symptoms of pancreatitis and the discovery of diabetes deserve special comment, because it is unusual for diabetes to make its appearance after such a brief history of pancreatitis. Among these five cases there were two in which a family history of diabetes casts some doubt on the assumption that the pancreatitis was the sole cause of the diabetes; two in which it was difficult to be sure of the duration of pancreatitis because of the virtual absence of pain; and one in which there had been a series of severe attacks with cyst formation within a period of about ten months which might reasonably have been expected to damage the pancreas sufficiently to give rise to diabetes. Certainly in the majority of cases there was a series of acute attacks over a considerable period before there was sufficient destruction of islet tissue to produce diabetes. In none of the cases did permanent diabetes result from a single attack of pancreatitis. This can be explained in part by the large functional reserve of the islet tissue and in part by the high mortality rate associated with acute hemorrhagic necrosis of sufficient severity to destroy a major portion of the pancreas.*

The course of the diabetes in these cases was characterized in general by a tendency to be transient or mild in the beginning, and to become permanent and increasingly severe as more and more of the pancreas was destroyed with the passage of time and with the occurrence of more and more exacerbations of the pancreatitis. Once permanent diabetes was established, it exhibited fluctuations in severity, the requirement for insulin rising and falling with exacerbations and remissions of the process in the pancreas. Probably the flare-ups of diabetes were due, not solely to diminished production of insulin by the pancreas during acute attacks, but also to a nonspecific aggravation of the disease such as may occur in any case of diabetes with almost any intercurrent illness, particularly a painful or febrile illness. The highest requirement for insulin recorded in any of these cases was 84 units per day, following an acute exacerbation of the process in the pancreas (case 2). In periods of remission between attacks the requirement for insulin rarely exceeded 30 units a day. In seven of the twenty-four cases insulin had never been necessary for control of glycosuria, and in two of the cases the diabetes was of such mildness that its presence was established only by means of glucose tolerance tests.

*Shumacker,[5] in an extensive review of the subject of acute pancreatitis as a cause of diabetes, described one case in which permanent severe diabetes developed in a man, aged twenty-seven years, in the course of an attack of acute hemorrhagic pancreatitis. There was no definite history of other attacks of pancreatitis preceding the one which produced diabetes, although there had been one other attack of abdominal pain of indeterminate nature requiring hospitalization. Shumacker estimated, on the basis of a survey of the literature, that in at least 2 per cent of all cases of severe acute pancreatitis diabetes develops. However, it is difficult to be sure that in all the cases on which this figure was based diabetes developed as a consequence of a single attack of acute pancreatitis.

5. Shumacker, H. B., Jr.: Acute pancreatitis and diabetes. Ann. Surg. 112:177-200 (Aug.) 1940.

Palliative surgical procedures, such as internal or external biliary drainage, which sometimes seem to prevent the occurrence of further flare-ups of pancreatitis, may cause the diabetes to become milder by permitting the inflammatory process in the pancreas to subside. An example of this was the case of a man, forty-five years old, having chronic pancreatitis with calcification and a pancreatic cyst, whose daily requirement for insulin decreased from 35 units to 10 units following cholecystogastrostomy.

One would anticipate that a destructive process in the pancreas which was severe enough to produce diabetes mellitus would usually be associated with evidences of external pancreatic insufficiency. However, among the twenty-four patients in this group, only eight had frank steatorrhea. It seems probable that many of the remaining sixteen patients had minor degrees of external insufficiency which might have been demonstrated by means of studies of fecal loss of fat and protein during periods of high dietary intake of fat and protein.

In those cases which were observed in the terminal stages of the disease, malnutrition was a common feature, due in part to loss of protein and fat in the feces, and in part to lowered food intake because of abdominal pain and digestive disturbances. Like starvation from any cause, this tended to ameliorate the diabetes and decrease the requirement for insulin. For example, a patient who had required approximately 40 units daily when he was well nourished recently returned in a poor state of nutrition and was found to require only 15 to 18 units daily.

Brief reports of two cases from this series illustrate the chronology of events with respect to diabetes in typical cases of chronic relapsing pancreatitis.

REPORT OF CASES

Case 1.—In 1927, the patient, a man twenty-seven years old, experienced the first of a long series of attacks of severe upper abdominal pain. In 1928, laparotomy was performed and the pancreas was found to be inflamed. From 1928 to 1935, inclusive, he experienced eight to ten attacks of severe abdominal pain each year. In 1935, when he was examined at the Clinic for the first time, he had been experiencing polyuria and polydipsia and had been losing weight for one year. He was found to have diabetes mellitus, which was treated with diet and 40 units of insulin daily. There was no family history of diabetes. About this time the stools became noticeably bulky and were found to contain excessive amounts of fat.

On surgical exploration of the abdomen, in 1935, the pancreas was found to be enlarged to three times normal size, and to be diffusely indurated throughout its extent. Choledochostomy and

cholecystostomy were performed, and the biliary tract was drained for a period of four months. There were no further attacks of acute pancreatitis. In 1936, a diagnosis of peripheral neuritis was made. The neuritis eventually improved, but subsequently recurred and in 1941, a diagnosis of diabetic neuropathy was made. In 1944, examination of the ocular fundi revealed evidences of diabetic retinopathy. The most recent examination was carried out in 1945, at which time diagnoses of diabetic neuropathy and diabetic retinopathy were again made, and in addition findings suggestive of intercapillary glomerulosclerosis were noted. The diabetes was reasonably well controlled with 18 units of insulin daily.

The foregoing case is of unusual interest because it is the only one in the series in which degenerative complications of diabetes mellitus, that is, neuropathy, retinopathy and probably intercapillary glomerulosclerosis, were observed.

Case 2.—The patient was a man, who was thrity-three years old in 1939, when he experienced the onset of attacks of severe upper abdominal pain. In 1941, an abdominal exploration was performed during the course of an attack of pain because of suspected intestinal obstruction. In July, 1942, during the course of an attack of abdominal pain, he was found to have glycosuria and hyperglycemia. He received insulin in doses as high as 84 units daily. Evidences of diabetes persisted after subsidence of the attack, and he continued treatment with diet and insulin. There was no family history of diabetes. In October, 1942, the upper part of the abdomen was explored and the pancreas was found to be extensively and diffusely enlarged and calcareous. Cholecystogastrostomy was performed. This procedure failed to prevent the occurrence of flare-ups of pancreatitis. In 1943, frank steatorrhea became apparent. In 1944, posterior gastroenterostomy was performed because of duodenal obstruction and gastric dilatation. When last seen, in 1945, the patient was having almost continuous upper abdominal pain and presented the picture of diabetes mellitus of moderate severity, external pancreatic insufficiency, malnutrition and dependence on narcotics. Only 18 units of insulin daily were necessary for control of the diabetes.

SUMMARY

Chronic relapsing pancreatitis was responsible for approximately 0.3 per cent of the cases of diabetes mellitus observed in the Clinic from 1939 to 1945, inclusive. Permanent diabetes makes its appearance in such cases usually after a prolonged series of exacerbations of the process in the pancreas, resulting in the destruction of a major part of the islet tissue. The diabetes tends to become more severe with flare-ups of pancreatitis and milder with the subsidence of attacks.

In seventeen of the twenty-four cases reviewed, insulin was necessary at some time for control of glycosuria. With the appearance of malnutrition due to external pancreatic insufficiency and lowered food intake, the diabetes is ameliorated. In one case degenerative complications of diabetes were observed.

CHRONIC RELAPSING PANCREATITIS: SURGICAL MANAGEMENT

John M. Waugh, M. D., M. S. in Surgery, Division of Surgery:

Unquestionably, chronic relapsing pancreatitis is much more common than is generally realized. The excellent work of Gambill, Comfort and Baggenstoss has focused our attention of late on the pancreas and the clinical diagnosis is being made earlier and more frequently. As they have indicated, conservative medical measures offer little or no hope of relief and usually the disease is progressive. At present, the only hope of relief is by various surgical procedures which vary with different forms of the disease and which, unfortunately, at best cannot often restore the pancreas to normal function because some of the pathologic changes are irreversible; however, surgical treatment will make it possible for the patient to live comfortably with his damaged pancreas with reasonable assurance that the disease process will not progress further.

The earlier in the course of the disease surgical exploration is carried out the better are the chances that conservative measures will prove adequate. All patients subjected to cholecystectomy should have careful exploration of the pancreas, and when associated disease is found the common duct should be opened and explored and T tube drainage instituted for six months to a year. It is a singular fact that many patients coming to our care with chronic relapsing pancreatitis have undergone cholecystectomy previously, usually without T tube drainage of the common duct, and it is our feeling that early institution of this latter procedure might have prevented progression of the disease. Conversely, when exploring the pancreas to confirm the clinical diagnosis of chronic relapsing pancreatitis, one should carefully explore the gallbladder, removing it if it is thickened and diseased or if stones are present, and should open, explore and drain (six months to one year) the common bile duct. Choledochoduodenostomy (side-to-side is preferable to end-to-side) has, in the Clinic series (Gambill, Comfort and Baggenstoss), proved to be the most efficient conservative surgical procedure and is the procedure of choice in those patients who do not have associated biliary disease and in whom the duct is of a size (1 cm. or larger) to permit anastomosis with facility.

If jaundice is present and it is found to be due to narrowing of the duct in the pancreas because of the associated inflammatory reaction (edema or stricture) choledochoduodenostomy is indicated. Occasionally the inflammatory reaction about the common duct may make its visualization hazardous or the duct may be so small that one is hesitant of opening it and using T tube drainage because of the possibility of the formation of stricture. Under those circumstances prolonged drainage of the gallbladder may prove sufficient, but this procedure is the least desirable of the conservative measures.

As the disease progresses, calcification will appear which, as in other organs, represents the end stage of the inflammatory process. This calcification occurs, for the most part, in the parenchyma of the gland and very little of it occurs intraductally. Occasionally in this stage of calcification, which may be localized to the head of the pancreas or may be diffuse, the patient has no pain. If so, no surgical treatment is indicated. If jaundice is present with or without pain, choledochoduodenostomy may well prove satisfactory.

In the stage of calcification frequently the pain is intolerable and most patients require frequent and large doses of morphine for relief. Often there is associated diabetes and insufficiency of external pancreatic secretion. Under these circumstances resection of part or all of the pancreas may be advisable, for such resection will relieve the pain as a result of removal of the diseased part and, at the same time, the patient's metabolic functions will not be embarrassed any more than they are already as a result of the inflammatory process.

Excision of a part or all of the pancreas should be limited to those patients with calcification in whom there is no evidence of subacute or active inflammation. From the technical standpoint pancreatectomy is difficult if undertaken when the inflammatory process is active because the gland does not separate readily from the superior mesenteric vein under these circumstances. Before considering resection it has been our practice to try more conservative procedures first, such as choledochoduodenostomy or choledochostomy by T tube, if there appeared to be any hope of avoiding resection with its higher operative mortality.

Those patients surviving resection of the head of the pancreas for pancreatitis have done well. For the most part, this procedure has been utilized for patients with calcification localized to the head of the pancreas and with intractable pain and varying degrees of metabolic disturbance. Usually resection of the head has not adversely affected any diabetes or faulty fat digestion which was already present.

Total pancreatectomy presents a different situation, however, and it has been our practice to advise this operation only when the pancreas is diffusely calcified, when intolerable pain is present and when

there are diabetes and marked reduction of pancreatic function. It would seem, under these circumstances, that the risk of total pancreatectomy is justifiable as otherwise these patients are total invalids requiring morphine, and absence of the pancreas should be of little consequence since its function is already severely damaged. Two patients have undergone total pancreatectomy for chronic pancreatitis at the Clinic and both have survived operation with complete relief of pain. Unfortunately, in both cases very late complications related to their diabetes developed two and a half months and sixteen months postoperatively, respectively, and the patients succumbed. Two other patients who underwent total pancreatectomy for islet-cell tumor are alive and well three and five years, respectively, after operation.

Because of the risk of partial and total pancreatectomy, thoracolumbar sympathectomy has been advised and used for relief of the pain associated with chronic pancreatitis. It would seem that this procedure should, for the most part, be reserved for those patients in whom the inflammatory process is in the end stage of calcification. Otherwise, if this procedure is used in the active stage of the disease valuable signs may be lost because of the absence of pain, which would possibly interfere with the early diagnosis of some deep-seated lesion such as a pancreatic abscess. Also, since it is known that not all patients with pancreatic calcification have pain in the end stage, it would hardly seem wise to advise thoracolumbar sympathectomy as a routine early in the course of the disease. It would also seem wise in every instance to establish the diagnosis by laparotomy, ruling out any associated disease of the biliary tract and exhausting any of the conservative procedures cited above before carrying out any nerve-severing procedure.

Thus far we have not resorted to thoracolumbar sympathectomy in any patient with this disease at the Clinic because it has been felt that such an extensive operation for pancreatic pain was unnecessary and that it would be better to precede such an operation by posterior splanchnic block with dolamin as a diagnostic procedure. This has been carried out on several patients by Dr. Lundy of the Section on Anesthesia with gratifying relief. If these patients continue to obtain relief for several weeks, as two have, with repeated injections of the splanchnic nerves with dolamin, we will advise these patients to submit to splanchnicectomy. Whether thoracolumbar sympathectomy or splanchnicectomy will prove more satisfactory than pancreatectomy because of the lower operative mortality will require a wider experience with all the procedures and a satisfactory postoperative follow-up over a considerable period.

CHAPTER III

STATE AND PROVINCIAL HEALTH ORGANIZATIONS[1]

By JOHN A. FERRELL

State and provincial health organizations, broadly speaking, have similar functions. They are distinct autonomous organizations developed to serve the health needs of their respective territorial jurisdictions and financed with public funds, for the most part appropriated by their respective legislative bodies, but no two of them are identical in composition. They all rank next in territorial importance to the national, dominion or federal health services, to which they are not subordinate, but the field of the one complements that of the other and certain health problems involve joint efforts. The federal authority includes international and interstate problems, whereas upon the state or provincial departments devolves responsibility for health matters within the State or province. Failure of the State to meet its responsibility will hamper the functioning of the federal service. Hence the federal agency has a real interest in aiding and strengthening the health service of the State or province. The federal agency, however, has no direct relationship with the local health organizations, be they for counties, districts, townships, or cities. The state agency does have a direct relationship to these local health jurisdictions but such relationship is not uniform and varies from a mere consultant status, upon invitation, to complete legal, administrative, and financial responsibility. The set-up—state and provincial—varies so much that an accurate and complete description of any one organization would not serve for others. The United States Public Health Service Bulletin No. 184 (1932, second edition, revised) describes each one separately. A revision of this publication is expected which will record growth, changes, etc., as of 1940. As changes may occur through actions by the legislatures which meet in a few States annually, in most States biennially, it would not seem advisable, in this publication which may not be revised frequently, to attempt to record current changes in particular States, but rather merely to present a brief, general description of the state and provincial health organizations. This statement accordingly is not intended to serve as a reference for special features of individual state or provincial health organizations. It is intended, however, that it shall convey a general impression of the common characteristics of the health services under consideration.

State Departments of Health.[2]—All state health departments have a chief executive whose title varies, and nearly all have boards of health with activities ranging from advisory services to executive functions. It seems desirable to consider first the board of health,

[1] In the United States and the Canadian provinces, with casual reference to other comparable governmental jurisdictions such as Alaska, Puerto Rico, Hawaii, and the District of Columbia.

[2] In general, unless otherwise specified, the statements made herein and the figures given are taken from Public Health Bulletin No. 184 (1932, 2d ed., rev.), United States Public Health Service. This, of course, applies only to data for the year 1930 and earlier years, with which the bulletin deals.

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then the health officer in his relation to the board, and to conclude with an account of the health officer's manifold duties.

Three States—Idaho, Nebraska, and Oklahoma—have no boards of health. A state health officer appointed by the governor is executive head of a department which has jurisdiction over public health matters. In each of six States—Connecticut, Maine, Massachusetts, New York, Ohio, and West Virginia—there is a public health council which functions mainly in an advisory capacity but serves essentially the purposes of a board of health. In four States—Illinois, Michigan, North Dakota, and Pennsylvania—there is an advisory council having a purpose somewhat similar to that of the public health councils. In all the remaining States there are state boards of health which vary as to responsibilities but for the most part have supervisory powers over state health activities, and make and enforce rules and regulations concerning public health matters not specifically covered by statute, such as regulations relating to quarantine and the combating of communicable diseases. In Alabama the state medical association, as represented by its Board of Censors composed of 10 members, constitutes the state board of health. In South Carolina the board is composed of 9 members—7 nominated by the state medical association and appointed by the governor, and 2 ex officio members, the state comptroller and the attorney general. In approximately 40 States the members of the board of health are appointed by the governor. The number of members ranges from 3 in Arizona and Florida to 15 in Georgia. About one-fourth of the States have 7 members. The length of the term for board members varies, corresponding in a few States with the term of the governor, but the term in approximately half the States is five or more years and so arranged that only one or two terms will end in a single year. This plan, which usually is basically bipartisan, is intended to make for a continuity of policy, stability, and a merit basis in filling positions.

As to qualifications for membership on the state board of health, wide variety exists. In 11 States all members must be legally qualified physicians. Twenty-one other States provide that one or more members shall hold degrees in medicine. At least 7 States provide that one or more members shall be engineers (sanitary or civil). In 10 States one member must be a dentist; in 4, a pharmacist, and 4 States require that one or more members be women. This wide variety in membership requirements for the board, in common with differences in other respects, serves to emphasize the fact that, if exact information is desired regarding a specific State, the record, such as may be found in Public Health Bulletin No. 184, or, preferably, in the publice health laws for that State, should be consulted.

The appointment of members of the state board of health is usually made by the governor, with nomination made in certain instances by state associations—medical, dental, pharmaceutical, engineering—or by the state senate. In certain States the law provides for one or more ex officio members.

The term of office of members in certain States corresponds with the term of the governor. In 35 States the terms are staggered in such a way that less than half expire in any year. Membership in most States is honorary and in many States the only expenses provided are those for travel in attending meetings. In 24 States the members receive a *per diem* ranging from $3.00 to $20.00, while in 19 States none is paid.

The usual variation prevails with regard to the frequency of meetings of the boards of health. For example, in 3 States one meeting annually is required; in 12 States, 2 meetings; in 15 States, 4; and in 10 States, 12. Provision is made in most States for calling special meetings. In quite a number of the States there are executive committees which meet more frequently than do the full boards.

Appropriations for state health services are made by the legislatures, in some cases to cover a line-by-line

budget, and in others, of general funds to be allocated by the boards of health on the recommendation of the state health officer for specific items and activities. The average per capita state appropriation in 1930 for the 48 States was 11.8 cents. New York then had a per capita appropriation of 40 cents. Within the past two decades the public health appropriations in most States have multiplied many times. In a few States the increase has been from $25,000 or $50,000 yearly to a budget of more than one million dollars, including funds from state and Federal sources. Yet in many States the funds now available fail to provide a health service which even approaches adequacy, according to the modern conception. The growth in appropriations has been so rapid and the changes so frequent that it seems inadvisable in a text of this kind to tabulate the health appropriations, by States. Tables I and II will, to a partial degree, give an impression of the magnitude of the health activities of the States in which the Federal Government co-operates.[1] Attention should be called to the Weekly Reports of the United States Public Health Service, which from time to time publishes the amounts of the respective state appropriations for public health. Public Health Bulletin No. 184 supplies data for years prior to 1931.

The powers and duties of state boards of health are set forth in the statutes for the respective States and they are far from uniform. Executive powers are vested in the boards in 4 States—Alabama, Colorado, Maryland, and New Mexico—whereas in 24 States they are vested in the state health officer who usually is ex officio secretary of the board. The boards usually may adopt rules and regulations for the protection of public health in situations not covered by laws. The fields of responsibility of the boards or of the executive officers will be more fully discussed later. In 9 States responsibility for the enforcement of the medical practice act is placed on the state board of health, whereas in the remaining 39 it rests upon other boards, commissioners, or agencies.

State Health Officer.—The executive officers of the state departments have no uniform title. Director, commissioner, superintendent, secretary, and health officer are a few of the titles employed. For the purpose of this discussion we shall employ "state health officer," the title used in about one-fourth of the States. He is chosen by procedures that vary. In half the States he is appointed by the governor, with or without the approval of the senate or board of health, whereas in nearly all the remaining States he is nominated or selected by the state board of health. In 22 States he serves as secretary of the board. In a number of States he becomes a member of the board as well as its secretary. His term of office is two years in 7 States, four years in 18 States, five years in 3 States, and six years or longer in the remaining States. Qualifications for the office vary. In 37 States he must be a qualified physician. In 2 States although the requirements do not state that he must be a physician they do specify that he must be skilled in sanitary science and have had public health experience. Usually all state health officers are physicians but 2 or 3 States have had for one or more terms executives who were not physicians. In 10 or more States the health officer must be licensed or registered to practice medicine in the State. In most States he must be, or must become, a resident, and in many States residence of five years or longer is a prerequisite. In 28 States experience in public health is a requirement. One State requires only

[1] The data shown in Tables I and II do not represent all the appropriations made for public health work by the state, Federal, and local governments in 1939, but merely cover state expenditures for activities which are being supported also by the United States Public Health Service and the United States Children's Bureau. The tables have been included in order to indicate the development and present magnitude of the activities of the state health organizations as compared with those of 1930, the year covered in Public Health Bulletin No. 184, from which most of the figures given in this article are quoted.

that he be a qualified citizen. Five States require no specific qualifications.[1]

The state health officer, with possibly two exceptions, is employed on a full-time basis and his salary ranges from about $2,500 to $12,000 a year, but most of the States pay in the $4,000 to $6,000 range. Necessary traveling expenses while on official duties, office facilities, and other essential expenses are, as a rule, paid by the State over and above the fixed salary.

Provincial Boards of Health and Executive Officers in Canada.—In Canada there are 9 provinces, as compared with the 48 States in the United States, but public health work in only 8 provinces is discussed here.[2] Each province has its own department of health which in general corresponds to the state department of health, but there are a number of important differences.

Only 4 provinces have boards of health in the usual sense. In British Columbia the prime minister and his cabinet may sit as a board of health, Nova Scotia and Ontario have no boards, and in Alberta the executive staff may sit as a board or council. All the remaining provinces provide for boards having 6 to 9 members, all, or the majority, of whom are physicians. The members of these boards are appointed in each province by the lieutenant governor in council and their terms of office range from two years to the pleasure or duration of the government. Their compensation is a *per diem* allowance. In one province, Saskatchewan, the board meets once yearly, three times in Alberta, twice in Manitoba, and four times in New Brunswick and Quebec. Appropriations are made by the provincial legislatures in support of detailed budgets in all provinces except Nova Scotia and Quebec, which receive lump sums which the boards allocate to the various activities. The per capita appropriations in 1930 averaged 25 cents, but in general they have been substantially increased since then. As they have undergone frequent changes it seems inadvisable to list the amounts for any single year. Although the per capita amounts for 1930 were given on p. 677 of Public Health Bulletin No. 184, they are so far out of date that any statement of accurate per capita appropriation in any province should be based on current information secured directly from the provincial health officer.

Executive authority in the provinces is vested in a minister of health. He is an elected member of the provincial legislature and as such is selected by the prime minister as a member of his cabinet. His tenure corresponds with the pleasure of the prime minister and the duration of his government. He delegates authority to the deputy minister of health who, theoretically at least, serves on a civil service or merit basis. The deputy minister usually functions as the executive officer and carries out the duties of his office. The deputy minister is supposed not to be changed when the government is changed but in recent years a number have been changed or displaced by a new government.

The provincial boards of health, like the state boards, usually may enact rules and regulations as to health protective measures which are not covered by existing legislation. The enforcement of the medical practice act is not delegated to the provincial board of health in any province; in Alberta, New Brunswick, Ontario, and Saskatchewan the College of Physicians and Surgeons is responsible, and in Nova Scotia the provincial medical board administers the act. The minister of health may or may not be a physician but all deputy ministers, except in Alberta and Saskatchewan, are required to be physicians or qualified medical practitioners, and certain provinces require that they hold diplomas of public health. The minister of health

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[1] For requirements for each State, *see* Public Health Bulletin No. 184 (1932), pp. 29–34.

[2] Data for Prince Edward Island are not included as its limited area and population make its problems differ somewhat from those of other provinces.

may hold portfolios other than for health, such as welfare, agriculture, labor, etc. The salary range for the deputy minister is from $4,000 to $6,000 yearly, the service is on a full-time basis, and, in addition, he is provided with office and facilities and with traveling expenses for official business.

The state and provincial health organizations have a wide variety of responsibilities which necessitates the formation of a number of subdivisions usually designated as divisions or bureaus. Each such subdivision in turn may constitute an organization of considerable size, having its own director or chief, its own special field of work, and a corresponding share of the public health appropriation to cover its cost. The number of divisions varies in the States and provinces but practically all have the following five: (1) central administration, (2) communicable diseases, (3) vital statistics, (4) public health laboratories, and (5) sanitary engineering. Moreover, the majority of States have practically all of the following divisions, but in certain instances two fields of activity are handled in a single division: (6) rural or district health work, (7) infant and maternal and child hygiene, (8) public health nursing, (9) public health education, (10) food and drugs, (11) industrial hygiene, and, in many instances, divisions for special diseases such as (12) tuberculosis, (13) venereal diseases, (14) malaria, etc. The size of the State as to population and area, its wealth, and the character of its public health problems determine to a large degree the size and complexity of the health organization. The same is true of its subdivisions.

Central Administration.—Functions of a broad and general nature which properly should not be delegated to special or technical divisions are handled in the central administration and are carried out by the state health officer or aids who serve on his immediate staff. In state health organizations having small budgets the health officer may also handle matters such, for example, as vital statistics or public health education, which usually are delegated to subdivisional units. Aside from his task of organizing the various divisions and giving them general supervision through their directors, the state health officer is spokesman of the entire organization in relationship with the governor, the state board of health, the public, the federal health service, on the one hand, and with the local health services on the other. He is responsible for the formulation of programs, policies, budgetary proposals, and laws, rules, regulations, etc., for their submittal for the consideration of the appropriate body, and, when duly authorized, for administering them directly or through his divisional heads. He usually retains in his office, as the division of central administration, all matters relating to personnel, and accounts which include the receipt and disbursements of funds for the entire organization. He passes upon all appointments, promotions, and dismissals, even though they may be suggested by division heads, giving approval or recommendation of the health organization to the body having final jurisdiction in matters of personnel, wages, budgets, etc., for the State. Other activities, such as purchasing all supplies for the department, preparation of the annual report, and its submission for approval to the state board of health, are also responsibilities of the central administration. In a few States, as Maryland, the personnel, accounts, and purchases are made the responsibility of a special division, but in such cases the state health officer has more intimate contact with this division than with other divisions. The proportion of the total state health appropriations employed by the central administration division varies widely from 100 per cent., in Wyoming and Nevada, to 3.2 per cent., in Colorado.[1] The general average cost for the central administration ranges from 10 to 20 per cent. of the total funds of the department.

[1] *See* Public Health Bulletin No. 184 (1932), p. 39.

As to the method for disbursing funds, 9 state health departments disburse all funds made available for their use, whereas in 31 States the state treasurer makes payments on vouchers prepared by the state health officer. Payment of the public health funds is made in 3 States by the auditor and in 4 States by the comptroller on vouchers originated in the central administration division or by the state health officer. In Michigan there is a state central accounting division. The purchase of supplies in 32 States is made through a bureau, or division, or agent not a part of the health department, but in 16 States this responsibility rests with the health officer or central administration division.

In Canada.—In the Canadian provinces the general scheme as to executive functions and the allocation of special functions to appropriate divisions is quite similar to that followed in the United States. Moreover, the responsibilities of the central administration division do not differ markedly from those assumed by this division in the States. The percentage of the total provincial appropriations for health employed in the central administration ranges from about 6 per cent. in Ontario to 79 per cent. in British Columbia. The range as to this factor is not so great as that in the United States, but there is no great difference in the general average. There is variation from province to province in the method for purchasing supplies, in the receipt and disbursement of funds, and in other features, but in all there appear to exist reasonable safeguards for the public funds.

Communicable Diseases.—The impelling motive for the establishment of health organizations was found in the desire to protect the people against communicable diseases, particularly those transmitted by direct personal contact and those which in the past have caused serious epidemics and frightful loss of life. This phase of the health work made necessary quite early two other special divisions of service, namely, vital statistics—birth, sickness, and death records—and the laboratory division to provide aid in diagnosing the diseases. The earliest activities of the communicable diseases division were directed against diseases such as yellow fever, smallpox, plague, cholera, diphtheria, etc. Quarantine was usually employed as the main protective measure except in the case of smallpox, for which the value of vaccination was known. With the growth of knowledge regarding the cause and mode of spread of many of the diseases and the laboratory methods for detecting them, the health program broadened and the work was placed on a more rational basis. Moreover, diseases such as tuberculosis, venereal diseases, malaria, typhoid, diphtheria, and hookworm disease were definitely embraced in the public health program. From time to time several other diseases have been added, and it is probable that still others against which measures for protection continue to be unsatisfactory will be included in due time.

The titles of the divisions of communicable diseases differ and the words "epidemiology" and "preventable diseases" are frequently included. Likewise, policy is not uniform as to the scope of the division of communicable diseases. In certain States the infectious, contagious, and certain other diseases are embraced, whereas important diseases such as tuberculosis and venereal diseases have special divisions. With enlargement of the program for the combating of communicable diseases as a result of new knowledge, the trend toward having special divisions for various communicable diseases has become more pronounced. Now nearly all the state and provincial health departments have such divisions. When the data for Public Health Bulletin No. 184 were prepared, the percentage of the total health appropriation applied to communicable diseases divisions—not including the cost for operation of hospitals for acute communicable diseases and for tuberculosis—ranged from 31.5 per cent. in South Carolina down to

1.5 per cent. in North Carolina, and the general average for the States was in the 7 to 14 per cent. range. Comments will be made later regarding tuberculosis and venereal diseases.

In any program directed toward the control of communicable diseases, uniform and prompt reporting of all cases and deaths is of the utmost importance. According to Public Health Bulletin No. 184, 34 States require the local health officer to report notifiable diseases to the state health officer. Eleven States require that the reports be made by the local health officer or by the attending physician, and in 2 States, Delaware and Louisiana, the physicians must report directly to the state health department. Certain diseases are reportable immediately, whereas others may be reported weekly or monthly. In general, except for the areas served by reasonably adequate local health organizations, the morbidity reporting is defective, incomplete, and consequently unreliable. This, in turn, applies to about two-thirds of the counties of the United States. In a few States emergency funds are available for use against exceptional epidemics but are not usable for the ordinary activities. In about one-third the use of such funds is discretionary with the governor. About two-fifths of the States have no emergency epidemic funds.

In the Canadian provinces the reporting of notifiable diseases, including epidemic diseases, varies as to exact procedure but the situation, in general, is quite similar to that in the United States. In organized areas the reporting of diseases is a responsibility of the local health officers and in the unorganized areas the provincial department functions as best it can. All provinces have an epidemic fund supplied by the provincial government for emergency use in combating serious epidemics.

Vital Statistics.—For the United States the registration area for deaths was begun in 1880 with Massachusetts, New Jersey, and the District of Columbia, and 19 cities included. The registration area for births was established in 1915. All or practically all state, city, and other governmental jurisdictions, such as the District of Columbia, are now in the registration areas and with the steady growth in state and local health organizations there has been more complete reporting. In most state health departments there is a division of vital statistics with its own director, aided by a staff sufficient to handle the work. The division of vital statistics is a subdivision of the state health department, except in Massachusetts where the secretary of state is the responsible head. The percentage of the total health appropriations required for vital statistics ranges from 2.4 per cent. in Delaware to 39.2 per cent. in Arkansas, averaging between 5 and 10 per cent. for the country. Cities, towns, and voting precincts are primary registration districts in all the States. In certain States in which county health organizations are in operation, the original certificate of birth or death, or a copy, may clear to the state registrar (the state health officer, or director of the division of vital statistics) through the county health department. In general, however, the certificates are forwarded by the local registrar to the state registrar. The local registrars are appointed in 6 States by the state board of health, in 8 by the state registrar, in 3 by the state health officer, in 5 by the local board of supervisors, in 5 they are selected as city or town clerks and as such are ex officio local registrars. In 20 States they are appointed by an official or board, or are elected by the people. In 44 States the local registrar receives a fee averaging 25 cents for each certificate recorded. The fees or other compensation are paid by the local government except in Florida, Arkansas, and Nevada where they are paid directly by the state department. There are in general use standard birth and death certificates, and the requirements as to birth and death reporting and burial permits are reasonably uniform.

The state department of health licenses physicians in 8 States, mid-

wives in 12 States, and undertakers in 6 States. In other states the licensing responsibility rests with other agencies.

In all provinces in Canada the registration of vital statistics is a function of the provincial department of health. The percentage of the total provincial appropriation employed by the vital statistics division ranges from 6.4 per cent. in Manitoba to 14.6 per cent. in Alberta. The registration districts are cities, towns, and villages except in British Columbia, where the district is the mining division, and in Quebec, the church parish. The local registrars are chosen by various methods in all provinces except Quebec where the priests are the local registrars in the Roman Catholic parishes, and the ministers or rabbis in other parishes. The registration fee received by the local registrar in Quebec is 15 cents; in Alberta, Ontario, and Saskatchewan, 25 cents; in Nova Scotia, 40 cents; and in Manitoba, one dollar. A salary or other basis exists in British Columbia and New Brunswick.

Public Health Laboratories.—The public health laboratory has developed within the past four or five decades, that is, since the discovery and identification of the respective causative micro-organisms for many diseases. Minnesota established a smallpox vaccine laboratory in 1890, and Rhode Island, a diagnostic laboratory in 1894. Massachusetts in the same year manufactured and purchased antitoxin for combating diphtheria. Gradually laboratories were established by other States and provinces. All States, with possibly one exception, and all provinces have provided for public health laboratory service. The scope of this service varies widely but all include facilities for the diagnosing of many communicable diseases. The laboratory service is conducted as a division of the state health department in nearly all States. In 3 States the laboratory is conducted as an activity of the state university, and in 7 the laboratory is operated by the state health department in buildings owned by the university.

In Canada the provinces have no common plan for laboratory service. In Alberta the university carries on the work with funds supplied by the provincial department of health. In British Columbia the principal laboratory is in a university building and is operated jointly by the provincial department of health and the Connaught Laboratory as a branch of the Connaught Laboratory at the University of Toronto. In Manitoba the laboratory is directed by the professor of bacteriology in the medical school and is located in a university building. The New Brunswick laboratory is located in a public hospital building in St. John, but is conducted by the provincial department of health. In Nova Scotia and Quebec the laboratories are housed in university buildings but are operated with health department funds. Ontario and Saskatchewan health departments operate their laboratories in parliament buildings in which other divisions of the health departments are housed. In general, the health authorities favor having the laboratory operated by the health department and lodged in the building which houses the other divisions of the health organization.

In addition to the diagnostic service which is an important function of all public health laboratories, the routine examination—bacteriologic and chemical—is provided for public water supplies, sewage, and milk. The manufacture of biologic products is an activity of several public laboratories, and a number engage to varying degrees in research. The diagnostic services provide tests for diphtheria, typhoid fever, gonorrhea, syphilis, rabies, intestinal parasites, malaria, etc., and usually biologic products whose value has been established are distributed. The supply is purchased from commercial or other manufacturers but about 25 per cent. of the laboratories manufacture one or more products.

In the United States, branch laboratories have been established in nearly half the States to expedite prompt receipt and examination of specimens. The percentage of the total health ap-

propriations expended on laboratory services ranged in 1930 from 2.6 per cent. in Wisconsin to 36.2 per cent. in Michigan, and in Canada from 8.1 per cent. in Manitoba to 17.8 per cent. in Alberta. In the United States the range most common was from 5 to 10 per cent. In most States and provinces all laboratory service is conducted under a single director but in a few instances separate laboratories are operated, one for diagnosis, and another for the examination of water, sewage, and milk. Some States producing biologic products have separate laboratories for the activity but in the laboratory services such as those for New York and Michigan all branches of the services are administered by a single director. The diagnostic services for syphilis have had phenomenal growth everywhere in recent years.

Sanitary Engineering.—Sanitary engineering is an important function carried on by a separate division in the health departments of 45 of the 48 States. The same is true of 6 of the 8 Canadian provinces; in the remaining States and provinces the general medical personnel of the department carries the responsibility. The growth in urban population and the seasonal movement of that population to rural areas for recreation have given rise to the rapid extension of sanitary engineering activities. The major responsibilities of the sanitary engineering division relate to safeguarding the water and milk supplies and to the protection of drinking water supplies, including lakes, streams, and harbors, against pollution. The sanitary engineer moreover has charge of measures for the installation and maintenance of drainage for health purposes, mosquito control, disposal of human, industrial, and other wastes, home sanitation, protective procedures for bathing pools and beaches, the abatement of nuisances, and many other activities designed to protect the public health. In the State of Kansas the health department and the university have established a co-operative arrangement for sanitary engineering.

The percentage of the state health appropriations expended for sanitary engineering ranges from 27 per cent. in Iowa down to 1.5 per cent. in Oklahoma, the range most common being between 6 and 14 per cent. Approximately the same holds true in the Canadian provinces. The scope of the engineering activities varies widely in different States. It is reflected to some extent by the size of the staff, the expenditures, and special problems. Aside from the customary control of the drinking water supplies and sewage systems, the engineering division enforces sanitary laws and regulations regarding the ice industry, bottled water, the sanitation of camp grounds, swimming pools, roadside water supplies. The bacteriologic and chemical examinations of specimens of water, milk, and sewage are usually made in the public health laboratories. In a few States the sanitary engineering division has its own laboratories separate from the general laboratory for diagnosis and production of biologic products. The frequency with which examination of water supplies is made varies widely but usually is determined in each State through experience.

Shellfish sanitation in the seaboard States is extremely important and usually is a responsibility of the sanitary engineering division. In Alabama and North Carolina the division enforces mandatory laws relating to sanitary privies. In the southern States the division engages in anti-mosquito measures directed against malaria. In general it concerns itself with the sanitation and ventilation of houses, and with screening as a health measure, and inspects the construction of dairies and the handling of milk.

Infant, Child, and Maternal Hygiene.—The state health departments are far from uniform as to their methods of providing for infant, child, and maternal care. Twenty-seven States in 1930 had separate bureaus or divisions of child hygiene. In 10 States in that year child hygiene and public health nursing were combined, 5 States had

divisions for maternal and infancy welfare, and in a few States the activities were carried on by other divisions, as in Iowa where the university conducted the activities and in Colorado where they were carried on through the State Department of Public Instruction. Generally, however, the trend has been for the state departments of health to have divisions of infant and maternal care which also usually include care for pre-school and, to some extent, school children. This trend has been more marked during the past two or three years since Federal Social Security funds for infant and maternal care and crippled children's services have been available to the state health departments through the United States Children's Bureau (*see* Table I). The percentage of the state health appropriations going to infant, child, and maternal hygiene ranged in 1930 from 2.5 per cent. in Ohio to 41.9 per cent. in New Hampshire, with the average slightly above 15 per cent. and corresponding closely with the customary percentage in other important divisions.

The activities in most States include maternal and prenatal work and, in a number of States, supervision and instruction of midwives, infant care, preschool hygiene, and school hygiene. Safeguarding infants against ophthalmia neonatorum is now emphasized by all health organizations—provincial, state, and local. In the southern States with their large Negro population, Negro midwives are used to a considerable extent in confinement cases. There the instruction and supervision of midwives is a real problem but the number of midwives is being diminished yearly and to an increasing degree physicians attend women in confinement. In the hygiene program for infants and children the public health nurse plays an important rôle. In nearly all States there is an orthopedic service, and many States have extensive dental hygiene clinics. School hygiene is handled by separate departments in 2 States and is a function of the department of health in 9 others. In general, in programs for the health and welfare of the pre-school and school child the education departments share in making plans, and in co-ordinating and supporting the work. In the field of mental hygiene there is in a few States a limited amount of activity directed largely to school children, but among most health authorities the opinion prevails that further research is needed to give to procedures definiteness and soundness which are now lacking. Until the nature of the problems becomes more tangible and there can be a more rational program health officers are disposed to concentrate on problems for which practicable and effective measures have been demonstrated.

In Canada the provincial health departments have all combined public health nursing and child welfare activities in a single division. The divisions in the provinces have functions similar to those of the corresponding divisions in the United States; but the scope of activities varies widely in the different provinces. Prenatal work is conducted chiefly through the local health organizations. The Province of Saskatchewan supplies financial aid to expectant mothers, $10 to the mother and $15 to the hospital or attending physician. Midwives are not very commonly used, although it is recorded that in New Brunswick they report 15 per cent. of births; in Manitoba and Saskatchewan they are not recognized at all. These two provinces and Alberta report licensing of maternity hospitals and orphanages, a function which in British Columbia and Ontario is handled by the provincial secretary. The provincial health department of Ontario operates a division of dental hygiene but presumably the work in other provinces has not developed to a degree warranting a special division.

Public Health Nursing.—In more than 40 States public health nursing activities are carried on by the state department in one division or another and all the provinces employ public health nurses but, as previously mentioned, they serve in the division of child hygiene. In 1930 the public

TABLE I

ALLOCATION OF FUNDS TO STATE HEALTH ORGANIZATIONS FOR 1939 FOR CRIPPLED CHILDREN SERVICES AND FOR MATERNAL AND CHILD HEALTH SERVICES BY THE UNITED STATES CHILDREN'S BUREAU AND ALSO FUNDS FOR THESE SERVICES SUPPLIED BY STATE, LOCAL, AND OTHER HEALTH AGENCIES *

State	Total	State	Local	Children's Bureau Services		Other Funds
				Crippled Children	Maternal and Child Hygiene	
TOTALS	*$14,045,012.90*	*$4,629,314.28*	*$1,413,790.44*	*$3,249,002.74*	*$4,285,794.31*	*$467,111.13*
Alabama	333,763.89	92,117.33	28,089.20	71,777.44	110,565.19	31,214.73
Alaska	89,259.79	14,903.56	16,093.00	5,220.48	48,641.63	4,401.12
Arizona	176,996.17	56,770.51	16,819.51	45,398.94	58,007.21	—
Arkansas	333,241.95	153,331.98	1,200.00	93,800.00	84,341.18	568.79
California	374,394.69	16,494.84	135,499.77	71,816.62	122,561.85	28,021.61
Colorado	196,450.79	59,459.46	18,200.00	44,459.46	67,060.84	7,271.03
Connecticut	207,882.40	97,831.20	—	54,000.00	55,026.70	1,024.50
Delaware	70,442.50	28,543.00	—	6,099.50	32,773.71	3,026.29
District of Columbia	214,389.02	78,274.46	—	56,171.84	51,528.27	28,414.45
Florida	249,056.21	77,336.86	24,691.82	40,299.91	105,326.92	1,400.70
Georgia	405,186.40	161,970.27	9,472.50	100,000.00	127,853.09	5,890.54
Hawaii	120,979.87	54,220.13	—	26,540.00	36,115.63	4,104.11
Idaho	147,916.74	36,491.73	27,400.48	29,230.00	54,794.53	—
Illinois	688,795.26	269,505.50	42,421.00	193,486.63	150,911.00	32,471.13
Indiana	384,581.97	39,757.00	143,906.01	101,730.00	94,707.14	4,481.82
Iowa	234,820.61	79,076.25	29,816.00	66,476.25	56,397.31	3,054.80
Kansas	268,841.59	89,297.98	30,104.00	54,860.00	92,619.61	1,960.00
Kentucky	331,931.84	98,984.35	50,963.11	81,112.62	100,871.76	—
Louisiana	166,574.79	14,115.83	45,450.15	—	104,278.36	2,730.45
Maine	208,813.99	68,730.67	6,169.00	45,811.71	71,757.22	16,345.39
Maryland	212,733.83	95,113.06	—	52,907.79	64,712.98	—
Massachusetts	371,018.03	155,244.98	—	91,645.67	86,402.94	37,724.44
Michigan	409,692.66	187,982.92	—	100,000.00	110,407.03	11,302.71
Minnesota	304,122.60	80,313.83	58,359.63	74,013.83	84,925.68	6,509.63
Mississippi	251,131.18	66,596.57	26,399.93	37,866.43	107,401.82	12,866.43
Missouri	351,529.54	86,986.10	77,059.17	63,446.10	121,005.02	3,033.15
Montana	174,028.37	56,000.00	19,803.48	45,500.00	52,476.63	248.26
Nebraska	156,405.17	71,188.38	—	54,496.48	30,189.03	531.28
Nevada	44,894.38	2,000.00	2,200.00	1,000.00	39,468.88	225.50
New Hampshire	97,515.66	35,172.50	—	11,900.00	44,029.07	6,414.09
New Jersey	365,552.13	92,207.88	76,985.79	105,092.50	84,479.25	6,786.71
New Mexico	198,284.66	49,710.00	24,068.79	41,070.00	80,603.31	2,832.56
New York	700,900.00	277,725.00	72,725.00	140,150.00	210,300.00	—
North Carolina	416,721.40	162,965.29	—	98,041.86	130,029.00	25,685.25
North Dakota	175,678.80	58,010.00	16,411.93	40,655.00	53,431.23	7,170.64
Ohio	494,023.27	174,703.40	61,710.68	131,255.40	119,983.76	6,370.03
Oklahoma	305,491.14	117,592.10	2,151.21	77,543.52	92,677.89	15,526.42
Oregon	219,691.12	65,126.73	22,431.50	52,275.00	67,869.86	11,988.03
Pennsylvania	643,765.08	286,723.03	—	168,763.72	153,118.82	35,159.51
Rhode Island	112,411.64	42,855.00	—	23,880.00	35,676.64	10,000.00
South Carolina	291,195.02	42,254.64	78,570.74	66,555.59	103,814.05	—
South Dakota	126,701.58	37,500.00	8,400.00	25,000.00	49,855.41	5,946.17
Tennessee	306,909.38	52,650.93	82,824.62	77,725.00	89,224.45	4,484.38
Texas	675,449.93	222,555.96	77,595.27	153,423.64	210,051.42	11,823.64
Utah	184,781.53	83,891.98	—	38,418.88	62,470.67	—
Vermont	107,194.77	32,616.66	6,320.33	18,635.19	43,027.40	6,595.19
Virginia	305,401.86	116,778.46	14,498.97	73,378.46	95,062.97	5,683.00
Washington	215,699.70	59,135.38	28,358.18	52,265.38	60,942.83	14,997.93
West Virginia	259,217.58	71,596.76	27,119.67	55,646.76	74,029.67	30,824.72
Wisconsin	292,009.70	128,903.83	3,500.00	73,159.14	76,446.73	10,000.00
Wyoming	70,540.72	30,000.00	—	15,000.00	25,540.72	—

* Data supplied by and used with permission of the United States Children's Bureau.

health nursing activities of the state health departments were carried on by separate divisions in 9 States, combined with child hygiene or infant and maternal care in 28 States, and were a function of the central office administration in 5 States. However, in state, and particularly in local, health organizations, the public health nurses outnumber the medical officers more than two to one. In administrative circles there continues to be uncertainty and difference of opinion as to the most effective administrative method for including public health nurses in the state and provincial health departments, but opinion uniformly recognizes that they are absolutely essential to health services, that they should be well educated academically, socially, and professionally, and that they should enjoy a responsible status as to both rating and compensation. The qualification standards for public health nurses have been gradually raised and undoubtedly this trend will continue. This in turn should simplify the administrative problem of the nurse's rôle in the central health organizations of the States and provinces. In the local health organizations, which the central organizations usually support, the policy is fairly definite and uniform.

Public Health Education.—Among the divisions of health departments the designation "public health education" should not be confused with professional education which relates to the training of public health personnel, mainly by universities. The objective of the public health education division is mainly to educate the public regarding hygiene and public health. It is expected to transform technical matter into simple language understandable by the laity, the school child, the teacher, and the public at large. The material should find a place in textbooks, in the press, in radio broadcasts, and in public health exhibits, through the use of the movie film and all other useful channels. Although the public health activities directed to the education of the public are steadily growing, they had, up to 1930, involved the employment of special personnel or the creation of special divisions, in only 17 States and two provinces, but with the growth in health organizations increasing attention is being directed to public health education. In 30 States and 7 provinces the responsibility was carried either by the central administration or one of the other established divisions. A close working relationship of the health department and department of public education is highly desirable and is to be observed in many States and provinces.

Food and Drugs.—The enforcement of the food and drugs laws is a state health responsibility in 19 States; in the remaining States it is handled by other departments, most commonly the department of agriculture, and in Canada for the most part it is a federal responsibility. In the United States 12 of the state health departments have special divisions for food and drugs, 6 of these having laboratories for testing the quality of foods and drugs and for adulterations, etc. In some instances the food and drug division carries on an inspection of hotels, bakeries, slaughter houses, cold storage warehouses, the shellfish industry, etc., but the plans and scope of activities vary widely.

The quality and safety of milk is, of course, of deep concern to every health organization, whether state or local. Usually the food and drug division or department of agriculture places emphasis on the food value of milk, whereas the health department in one or another division (frequently sanitary engineering) attempts to safeguard against contaminated milk as a medium in the spread of communicable diseases, such as typhoid fever, dysentery, undulant fever, septic sore throat, etc. The progress made in the United States and Canada during the past two decades in safeguarding the public water and milk supplies has been phenomenal. Generally one can travel from coast to coast and partake safely of water and milk except for the sup-

plies in rural homes and villages where community regulations do not apply.

Industrial Hygiene.—The growth of industrial activities in the United States and Canada has led the health authorities to enlarge their programs of health protection, specifically for the industrial workers and their families. Concurrently, to an increasing degree, the industrial corporations have voluntarily set up facilities for the protection of their employees from occupational hazards and diseases. Moreover the movement has had the support of labor organizations. The United States Social Security funds [1] for public health enabled the United States Public Health Service to co-operate financially and otherwise in extending industrial hygiene measures. This has enabled about three-fourths of the state health departments to develop or enlarge their divisions of industrial hygiene. In Canada the provinces of Ontario, Quebec, and, to a lesser degree, Alberta, have established and operate divisions of industrial hygiene. An important feature of these divisions is the instruction of the workers and their families as to occupational dangers to health and as to protective measures. This work and the general "safety" campaign has led to a marked reduction of sickness, accidents, and deaths in the field of industry.

General Considerations.—Having given above a very general account of the organization of the state and provincial departments of health, and of the major divisions under which their work is organized, it seems desirable now to deal briefly with a number of subjects not discussed separately for each division. For example, certain diseases such as tuberculosis and syphilis are problems of such magnitude that they individually justify divisions separate from the divisions of communicable or other preventable diseases.

TUBERCULOSIS.—Although the tuberculosis death rate has been halved in recent times, it is still responsible for a large percentage of the deaths and of sickness, as the disease comes on insidiously and is generally a chronic malady that can best be treated in sanatoria. Prolonged activities in the homes and in the hospitals by a large force of workers are required, and the cost to the taxpayers is enormous. The fight against tuberculosis was undertaken by the National Tuberculosis Association in 1904 and continued for some time as a task of this private agency. Gradually the responsibility was assumed to a large degree by state governments but the method of transfer was not uniform. By 1930 29 state departments of health had assumed definite responsibilities in connection with the prevention and control of this disease. Fourteen of these States had bureaus or divisions specifically for tuberculosis and in the others it was handled by the division of preventable diseases or by the central administration. Nineteen state departments of health in 1930 reported no special activities in tuberculosis control. This should not suggest, however, any lack of effort by the local health organizations in such States and by the tuberculosis associations. About one-third of the States operate mobile field clinics, and most of them have portable x-ray equipment as a diagnostic aid. They operate with and through such local health organizations as exist. Nine state health departments operated (1930) 18 tuberculosis sanatoria. Not all state-supported tuberculosis sanatoria are operated by departments of health and many tuberculosis sanatoria are operated by local government. In only a few States is the number of beds for tuberculosis patients nearly adequate. Strengthening of the tuberculosis facilities is urgently needed in more than one-third of the States, and the Federal Government may have to give substantial financial aid before it will be possible to correct conditions. State subsidies toward county-owned and operated tuberculosis sanatoria are reported for California, Massachusetts, Michigan, Minnesota, and Washington.

[1] *See* Table II.

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SYPHILIS AND GONORRHEA.—The venereal disease problem is extensive in all of the States and provinces. These diseases have spread insidiously like tuberculosis and likewise they are chronic and in every particular expensive to treat and to cure. Because of the public attitude toward syphilis and gonorrhea it has been difficult to get the subject into the open and to conduct public educational activities. Recently, however, aggressive health authorities have overcome this public attitude. Facts about the costs of these diseases in life and health, how they are contracted and how they can be prevented and cured, have been broadcast, with the result that in addition to the state and local appropriations to combat these diseases the Federal Government supplied to and through the state departments of health $2,292,215 for the year 1939 (Table II). Diagnostic laboratories have been enlarged and new ones established. Clinics for patients have been opened and staffed. In its fight against syphilis the North Carolina State Department of Health is aided with more than $150,000 yearly by the Reynolds Foundation.

In Canada, the fight against syphilis likewise is being stimulated by dominion appropriations to the provincial health departments and the provinces are increasing their appropriations. The general plan of operation is similar to that in the United States. Although the measures against syphilis are reasonable, rational, and definite, it is not easy to measure progress in bringing the disease under control, but it is expected there will be much tangible evidence of its reduction in a few years.

MALARIA.—In 6 or 8 southern States malaria is a health problem of sufficient importance to warrant the organization of special divisions in the state health departments to combat it. Screening, drainage, and therapeutic measures are employed. In urban areas where the population and wealth concentrated in a limited area are sufficient, effective control measures are usually feasible, but the malaria problem in the rural communities continues to be baffling. It is mainly an economic matter because the disease can be controlled almost anywhere if sufficient funds are available. Other tropical and subtropical diseases, such as hookworm disease and dysentery, are also problems in the southern States.

SALARIES IN STATE AND PROVINCIAL HEALTH DEPARTMENTS.—Salaries of state health officers range downward from $12,000, paid in New York. The arithmetic average salary is $5,665. Eighteen of the state directors, or 37.5 per cent., receive salaries above this amount and 62.5 per cent. of them are below it. In Canada, the corresponding provincial executives, the deputy ministers of health, are paid from $4,000 to $6,000 yearly.

Division chiefs in the state health departments of the United States are paid from the maximum of $9,000 yearly (laboratory director in New York) downward. The arithmetic average for salary of director of epidemiology is $4,282 for 33 States; $3,538 for vital statistics for 31 States; $4,133 for laboratory directors in 43 laboratories; $3,960 for directors of sanitary engineering for 43 States; $3,544 for directors of child hygiene in 37 States. The salaries for all grades of service are pitiably small in a number of States and provinces but generally the appointments are being made more and more on the basis of merit, professional training, and experience. This, in turn, makes for public confidence, security of tenure, and higher compensation. Unfortunately there are still a number of important sore spots where conditions are far from satisfactory, and it is obvious that they will not be quickly corrected, but gradually we may expect to see the number diminished.

TRAINED PERSONNEL FOR HEALTH SERVICE.—The State and Territorial Health Officers Conference endeavored to set up qualification standards for all kinds of public health personnel. During the past two decades courses of training have been organized

TABLE II

AMOUNTS BUDGETED BY STATES FOR PUBLIC HEALTH WORK UNDER THE PROVISIONS OF THE SOCIAL SECURITY AND VENEREAL DISEASE CONTROL ACTS, FISCAL YEAR 1939 *

State	Total †	State †	Local	Public Health Service		Other Agencies ‡
				Social Security Act	V. D. Control Act	
TOTALS	*$50,918,164.40*	*$22,425,374.02*	*$12,879,125.28*	*$9,669,573.34*	*$2,292,215.74*	*$4,151,876.02*
Alabama	1,544,239.20	466,866.08	613,719.20	249,785.00	72,294.00	141,574.92
Alaska	177,715.04	60,906.35	3,443.00	37,324.69	2,701.00	73,340.00
Arizona	235,198.53	48,645.00	82,125.00	57,170.95	9,639.00	37,618.58
Arkansas	686,821.42	224,440.00	103,046.00	252,480.42	46,750.00	60,105.00
California	1,352,979.83	248,661.17	495,782.66	354,121.00	103,791.00	150,624.00
Colorado	310,013.75	72,180.00	42,451.75	141,954.00	18,228.00	35,200.00
Connecticut	1,020,609.96	310,241.00	571,241.71	112,609.25	26,518.00	—
Delaware	175,625.49	110,050.00	26,788.00	30,504.49	5,283.00	3,000.00
District of Columbia	599,634.10	499,510.00	—	83,084.10	16,860.00	180.00
Florida	711,202.12	233,943.72	172,413.00	144,927.28	38,055.00	121,863.12
Georgia	1,671,515.90	579,619.04	580,910.30	300,161.17	77,134.00	133,691.39
Hawaii	517,404.13	437,483.97	1,800.00	69,520.16	8,000.00	600.00
Idaho	305,643.26	100,065.00	44,680.00	77,910.34	8,019.00	74,968.92
Illinois	1,425,394.88	426,697.12	386,733.00	469,862.10	123,182.66	18,920.00
Indiana	747,403.47	291,293.48	113,373.16	248,523.51	58,541.32	35,672.00
Iowa	556,515.34	115,769.50	61,307.00	197,760.09	41,564.00	140,114.75
Kansas	475,105.37	141,987.87	160,746.50	131,032.00	31,659.00	9,680.00
Kentucky	1,203,871.38	524,846.57	272,991.77	245,930.28	57,318.00	102,784.76
Louisiana	1,496,083.38	900,000.00	272,667.26	185,817.76	50,871.00	86,727.36
Maine	379,508.86	209,893.00	22,416.00	76,843.86	13,486.00	56,870.00
Maryland	1,601,653.53	456,220.50	897,677.00	141,895.79	31,892.00	73,968.24
Massachusetts	3,937,278.37	3,402,305.00	28,415.00	248,672.37	69,623.00	188,263.00
Michigan	1,413,056.99	523,270.00	529,518.70	245,762.00	75,891.29	38,615.00
Minnesota	1,014,604.51	294,962.24	466,027.08	192,822.73	40,012.46	20,780.00
Mississippi	817,561.21	204,458.63	289,768.38	198,979.92	54,743.50	69,610.78
Missouri	769,268.16	152,716.00	212,845.99	293,061.22	59,365.00	51,279.95
Montana	275,682.83	65,746.00	68,875.98	66,969.00	8,575.00	65,516.85
Nebraska	206,041.57	34,148.57	8,280.00	113,320.00	22,833.00	26,960.00
Nevada	69,776.16	24,576.16	—	41,450.00	—	3,750.00
New Hampshire	272,695.63	85,725.00	72,894.00	55,445.29	8,775.00	49,856.34
New Jersey	2,109,424.70	497,955.00	1,199,769.89	251,700.80	71,327.00	88,672.01
New Mexico	403,158.20	64,880.00	171,690.00	73,206.50	9,023.00	84,358.70
New York	7,001,764.79	5,538,990.79	268,320.00	656,480.00	193,724.00	344,250.00
North Carolina	1,895,255.78	370,840.07	890,836.52	346,412.36	84,259.00	202,907.83
North Dakota	280,619.75	51,373.23	53,284.82	111,333.20	12,340.00	52,288.50
Ohio	1,486,217.72	244,750.02	641,241.37	373,626.89	102,576.81	124,022.63
Oklahoma	665,967.95	283,183.12	55,708.59	202,762.10	46,342.00	77,972.14
Oregon	386,794.06	50,797.00	183,949.00	104,137.56	16,077.00	31,833.50
Pennsylvania	2,540,913.24	1,581,102.21	—	508,006.00	165,082.00	286,723.03
Rhode Island	347,730.33	219,545.00	—	60,068.33	12,062.00	56,055.00
South Carolina	965,088.94	194,112.00	273,022.54	197,272.72	52,522.00	248,159.68
South Dakota	152,407.38	28,525.00	19,950.00	80,636.38	9,156.00	14,140.00
Tennessee	1,184,844.78	283,033.93	407,104.16	305,937.35	66,644.00	122,125.34
Texas	1,715,961.29	313,557.25	680,405.99	415,891.54	96,601.70	209,504.81
Utah	231,325.00	83,887.00	34,841.00	62,094.00	9,183.00	41,320.00
Vermont	170,124.13	55,000.00	11,480.00	52,796.45	6,286.00	44,561.68
Virginia	1,364,253.00	795,668.00	240,122.00	233,180.00	58,983.00	36,300.00
Washington	626,110.78	125,082.00	252,621.46	153,111.11	25,358.00	69,938.21
West Virginia	644,312.50	157,240.00	209,055.50	172,380.00	32,297.00	73,340.00
Wisconsin	727,577.46	222,660.43	182,785.00	212,596.03	40,768.00	68,768.00
Wyoming	48,208.25	15,965.00	—	29,743.25	—	2,500.00

* Table supplied by and used with permission of the United States Public Health Service.
† Amounts shown do not include all State appropriations.
‡ Includes certain amounts budgeted by the United States Children's Bureau, and from other sources.

by universities in many regions of the United States and Canada. For the past two or three years there have been graduated annually from 10 universities approximately 100 physicians in public health, from 17 schools about 500 public health nurses, and from 12 universities nearly 100 public health engineers. From 50 to 100 other people such as chemists, bacteriologists, statisticians, etc., have also been graduated yearly. It seems that this number must be increased considerably for the next ten or fifteen years if the prospective needs for personnel are to be satisfied. Moreover the quality of the courses should be improved. About a million dollars yearly of public funds are being applied to aid the present and prospective health workers to take professional training but practically no increase in funds has been made so far to aid the universities to enlarge their teaching facilities. This phase of the training problem is of deep concern to the state health officers, and they are seeking means for remedying it. They are giving thought, also, to the modification that is needed in the present course of training for physicians and medical specialists, and for nurses who are to be employed in public health work, with a view to fitting them for the services they are expected to render. Moreover, there seems to be need for modifying the present courses for health officers and public health nurses with a view to their fitting in harmoniously with those who are or may be engaged in supplying medical care in close relation to or under the general supervision of the state health departments. The state health executives are resolved to safeguard the quality of all services that may be conducted under their supervision, be these services preventive or curative. They recognize that the success of this objective involves the establishment and enforcement of suitable qualification standards for all professional personnel.

RELATIONSHIPS OF STATE AND PROVINCIAL HEALTH DEPARTMENTS WITH FEDERAL AND LOCAL HEALTH SERVICES.—Territorial areas such as the District of Columbia, Puerto Rico, Alaska, Hawaii, Guam, the Virgin Islands, and the Panama Canal Zone are not independent States of the United States but its dependencies. The health service in each territory is made to conform to the general plan of government that is operating in each area and if not administered directly by the United States Public Health Service each is nevertheless a charge of the Federal Government and as such should be included under the chapter for Federal Health Organizations. In passing it may be said that the District of Columbia health organization is quite similar to city health organizations, that for Puerto Rico is quite similar to a state health organization, whereas the health services of the other territories are not similar to either city or state organizations. There are no regional health organizations in the United States or Canada which involve a merging or consolidation of the health services of two or more of these jurisdictions. The nearest approach to a regional organization is the Tennessee Valley Authority which embraces part of several States along the valley of the Tennessee River. It works with the respective state health organizations which continue to have full jurisdiction in health matters throughout the States. Any health district within a State or province involving the merging of the health resources of two or more local governmental jurisdictions (counties, township, municipalities, etc.) should be regarded as a local health organization.

RELATIONSHIP OF STATE AND PROVINCIAL HEALTH SERVICES TO THE FEDERAL HEALTH SERVICE.—The States and the provinces are, to a large degree, autonomous but of course they are not directly responsible for measures that are international or inter-state in character. Nevertheless in the field of public health their interests involve full co-operation with the Federal Government in making these services effective. Moreover, since the national health responsibilities cannot be discharged effectively unless the health services of the

States and of their subdivisions are effective, and since these subdivisions in many cases, in fact usually, are unable to finance adequate health services, the Federal Government in the United States supplements the funds supplied by the States by large appropriations for specific activities, such as those made through the United States Public Health Service and the Children's Bureau (*see* Tables I and II).

Relationship of State and Provincial Health Services to Local Health Organizations.—Many of the larger cities operate under special charters and are autonomous in most health procedures. However, in certain respects the state health department has complete jurisdiction for the entire State, including cities, in such state services as morbidity, mortality, and birth reporting. Except for the cities, the States are composed of legal governmental jurisdictions known as counties or townships, and, in certain provinces, as municipalities. The degree of the state or provincial health department's responsibility for health service in the smaller jurisdictions varies widely. Where the local government has no health service or where the local health service fails to safeguard the public health, the central or state authority may and often does assume or carry out the responsibility, and in many States the local government has to meet all or a part of the cost.

Regardless of how responsibility may be divided between the state and local government, the State cannot legally fulfill its responsibility unless the local health services are effective. Accordingly, the States frequently supply aid to the local health services for reasons similar to those which lead the Federal Government to aid the States. The state aid may take the form of money or personnel, or both. The working relationships in many instances are in accordance with agreements between the state and local agencies. Excepting the larger local health organizations, which are comparable to city health organizations, the local units employ personnel—health officers, public health nurses, and sanitation officers — for generalized services, but they are unable independently to finance specialized services such as public health laboratories, epidemiology, infant, child, and maternal hygiene, and specialists for tuberculosis and syphilis. The States usually supply these services to complement the generalized local services. Moreover, because of legal jurisdiction or substantial support in money, or personnel, or both, the state health department in most States supervises the local units and requires them to maintain desirable standards for personnel and service, and the local departments make reports of activities and finances to the state department.

Conclusion.—The reader who may desire fuller information regarding any state or provincial health organization than is given above is referred again to the specific health department or to Public Health Bulletin No. 184 (1932). Moreover, other bulletins and reports by this service and by the United States Children's Bureau will give up-to-date information regarding personnel, budgets, and important changes which occur from time to time. A number of text or reference books are on the market which give information regarding state and provincial health organizations.

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VI. CYTO-ARCHITECTONIC ALTERATIONS

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VI. CYTO-ARCHITECTONIC ALTERATIONS

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The possible cause of residual posttraumatic nervous symptoms has long been the subject of discussion. Variance in opinion as to the origin of these manifestations has given rise to two schools of thought. It is held by one school that such symptoms are largely of psychogenic origin and are the direct result of mental and emotional shock incident to the injury. The second group, on the other hand, believe that posttraumatic manifestations are due predominantly to organic lesions of the brain, although the character and distribution of such lesions have not been clearly established. It was our interest in this question that led us to begin what has proved to be a rather prolonged investigation of the changes in the elements of the brain following severe injury. While it is recognized that a study of morphologic changes could scarcely be expected to explain so variable a clinical picture, it was hoped that a more comprehensive and accurate conception of the alterations occurring in the nerve elements would at least enlarge our views in this respect.

As a result of our studies as a whole, an important concept has gradually taken shape—that injuries to the head tend to result in changes in the brain of two types. One of these changes is general and is a result of the force of the blow. The other is more typically local, the location and character of the lesion being a combined result of the mechanism of the injury and the anatomic characteristics of the injured region. To be sure, the dividing line between the two types is not always sharply drawn, but in the main they are sufficiently characteristic to be distinguished one from the other.

The general changes are largely physiologic rather than morphologic, although their effects may become apparent in the cerebral tissues if sufficiently marked. Loss of consciousness following the injury and edema of the brain are examples of this general change. Unconsciousness itself is not accompanied by any recognizable change in the cortical

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nerve cells so far as we can discover and is probably to be explained on the basis of a physicochemical change of reversible character in the colloids of the cell. Generalized impairment of vasomotor control, which results in edema, may become evident if the process is advanced. This is indicated grossly by flattening of the convolutions and decrease in the number and size of the oligodendroglia cells. The facile absorption of tissue fluid by these cells probably protects the parenchyma of the brain from the effects of hydration, whatever these effects may be. The increased amount of free fluid, so characteristic of posttraumatic states, is probably due to increased transudation into the perivascular and subarachnoid spaces and into the ventricles. The increased vacuolation of the choroidal and the ependymal epithelium and the distention of the pericellular and the perivascular spaces are presumed evidences of such activity.

The local effects of injury to the head, resulting in characteristic structural alterations, are to be seen in cases of contusion and laceration of the brain. Within the injured area the cerebral tissue is macerated and disintegrated, the nerve elements being completely destroyed. As a result of removal of the decadent tissue by phagocytosis and repair by the astrovascular elements, a scar is produced. If there has been extensive injury of the overlying dura so that fragments of its tissues have been implanted into the cerebral wound, the scar may contain an abundance of connective tissue. With contraction of this type of scar, local contractures and deformities are likely to result. On the other hand, after a typical contusion the damaged cerebral tissues and intermingled blood clot are removed *en masse* as the clot breaks down, leaving a comparatively smooth-walled defect. Only feeble adhesions to the dura develop at the margin of the wound if the arachnoid is torn, and these are incapable of regional distortion. The injury, therefore, results in loss of function of the nerve elements within the contused area, either directly through the destruction of nerve cells or by interruption of connections of other cells with this area. The loss of this function may not be detected on clinical examination.

MATERIAL AND METHODS OF STUDY

In this phase of our investigation the material used was much more extensive than that utilized in previous studies. The brains of 309 persons with injury to the head have been studied in the Ramón y Cajal laboratory since the original histologic studies were undertaken. Two hundred and twenty-nine instances of cerebral contusion were noted. It was from this group that material was selected for study of the architectonic alterations of the cerebral and the cerebellar cortex after trauma.

For the most part frozen sections were used. The usual staining methods were utilized with success, since we were concerned for the moment only with the disturbance in the arrangement of cells and not with alterations in their structure. At

times the use of metallic methods for the demonstration of nerve fibers and neurofibrils have proved to be of value. The usual methods for the demonstration of Nissl's substance have also proved to be worth while.

In the study of posttraumatic changes in the nerve cells we have chosen to consider the subject under two general headings: (1) changes in the cortical architecture and (2) alterations in structure of the nerve cells. In this report we have limited ourselves to a consideration of the architectonic disturbances, leaving the more detailed changes in the cells for another contribution.

NATURE OF CORTICAL INJURIES

A traumatic lesion of the cortex or subcortex is the composite result of the size and consistency of the injuring agent, the intensity of the force with which it is applied to the skull, the mechanism of its application and the anatomic peculiarities of the affected region. The actual production of the lesion which one sees at operation or at autopsy is the result of both primary and secondary factors. The actual thrust of the convolution against the interior of the skull results in the original bruise, and this effect is primary. This original injury is accompanied by rupture of many local blood vessels, and the resulting hemorrhage plays an important rôle in producing the ultimate lesion, not only in architectural changes but in the chemical reaction of the nerve tissues themselves, as our next study will emphasize.

For our purpose in this connection, cortical lesions may be divided morphologically into three groups: (1) areas of cellular necrosis, (2) contusions and (3) lacerations. The first type of lesion is invariably microscopic; the second may be either microscopic or macroscopic, while the last is invariably a gross injury. Each of these lesions will be considered in turn.

AREAS OF CORTICAL NECROSIS

In the course of previous investigations, the occurrence of small circumscribed acellular or relatively acellular areas was noted.[1] For the most part these areas were observed in the vicinity of cortical contusions and were apparently of vascular origin. Some of them represented areas of focal hemorrhage in which the red cells were not apparent or had disappeared in the evolution of the lesion (fig. 1). In other instances such areas were noted in the vicinity of contusions but were not due to the small accompanying hemorrhages (fig. 2). Their proximity to these hemorrhages, however, suggests a vascular origin.

1. Rand, Carl W., and Courville, Cyril B.: Histologic Studies of the Brain in Cases of Fatal Injury to the Head: IV. Reaction of the Classic Neuroglia, Arch. Neurol. & Psychiat. **27**:1342 (June) 1932. The photomicrograph shown in figure 15 should be noted.

At times such areas occurred in the absence of any evident hemorrhage. In some instances, especially when the subcortical white matter was involved, the lesion was evidently a small infarct. In other cortical lesions these acellular foci resembled the so-called *Herde* described by German investigators.

The etiology and mechanism of production of these areas of cortical necrosis have been a subject of much interest to neurohistologists. They have been observed in a variety of conditions. Perhaps the most helpful studies in their interpretation are those concerned with asphyxia. After

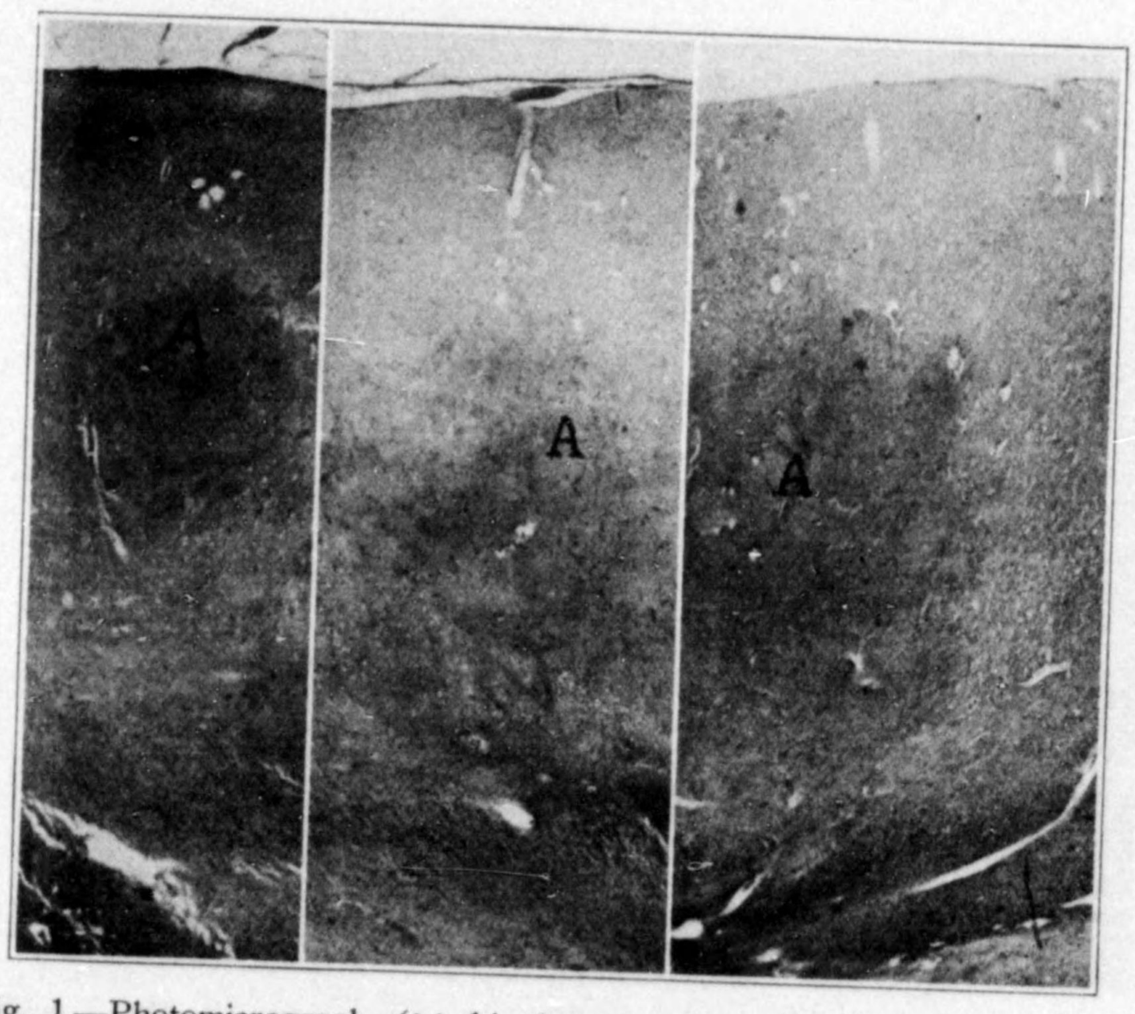

Fig. 1.—Photomicrograph (× 14; hematoxylin and eosin stain) of sections of the cortex, showing discolored acellular areas (*A*), due to grossly invisible petechial hemorrhage. The nerve cells in the margin of the hemorrhage are accentuated, owing to the presence of hematogenous pigment in their cytoplasm.

ligation of the major blood vessels in experimental animals Gildea and Cobb [2] noted these characteristic areas in the cerebral cortex. This seems to indicate that these "acellular" areas are the result of local asphyxia; in fact, they appear to be the characteristic lesion of asphyxia. In a recent study by one of us (C. B. C.),[3] in which sections of the

2. Gildea, E. F., and Cobb, Stanley: The Effects of Anemia on the Cerebral Cortex of the Cat, Arch. Neurol. & Psychiat. **23**:876 (May) 1930.

3. Courville, Cyril B.: Asphyxia as a Consequence of Nitrous Oxide Anesthesia, Medicine **15**:129 (May) 1936.

brain were studied in cases in which there was fatal termination after a respiratory crisis during nitrous oxide anesthesia, these pale areas, affecting one or more of the cellular layers of the cerebral cortex, were almost invariably present. In these cases it has been assumed that this lesion is evidence of asphyxia. On the basis of this assumption it is likely that when this lesion is present it is presumptive evidence of asphyxia, although, to be sure, the actual mechanism of its production is not always clear.

In order to determine more definitely the incidence and character of this interesting lesion so far as its relation to cerebral injury is con-

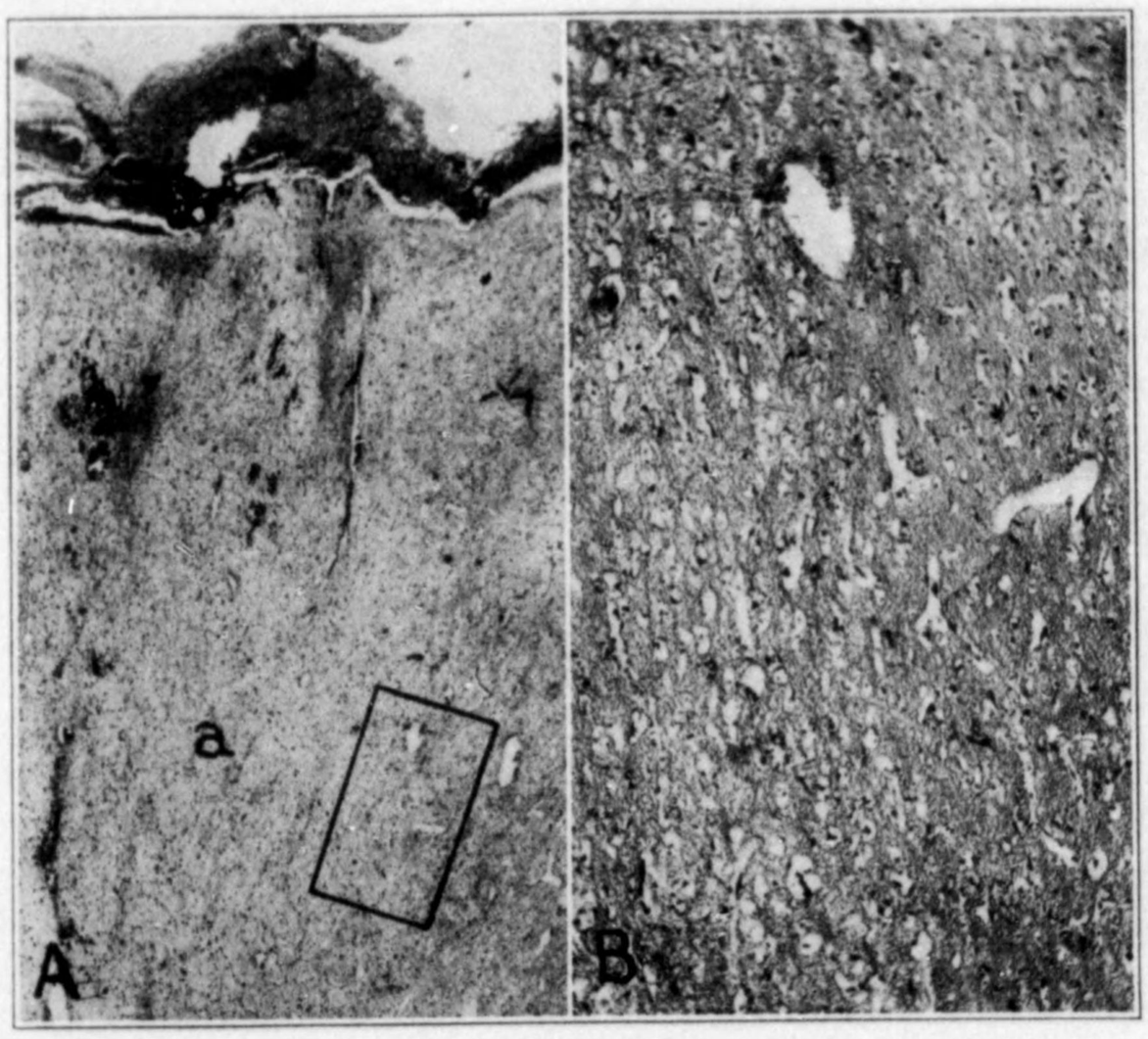

Fig. 2.—Photomicrographs (hematoxylin and eosin stain) showing (*A*) an acellular area (*a*) adjacent to a lesion of cortical contusion, which resembles a focus of cortical necrosis due to asphyxia (× 18), and (*B*) a more detailed view of the margin of the area, showing enlargement of the pericellular and perivascular spaces and sclerotic changes in the nerve cells, which are characteristic (× 65).

cerned, a special study was made of a series of 18 consecutive cases in which an injury to the head had been sustained. Blocks were taken from symmetrical locations in the frontal, parietal, temporal and occipital portions of the cortex, the basal ganglia of the cerebral hemispheres and the cortex of the cerebellar hemispheres. The patients from whom

the tissues were obtained had survived for intervals varying from two and one-fourth hours to seventy-four days. All varieties and degrees of cerebral traumatic lesions were to be observed in the group. In the brain of only one of these patients were areas of cortical necrosis of this type observed.

A Mexican woman, aged 58, had survived the injury for only six and one-fourth hours. She had been struck by an automobile and sustained a small laceration of the right side of the forehead. She was admitted to the hospital in coma and a state of shock, evidently due to fracture of the right humerus and the right tibia.

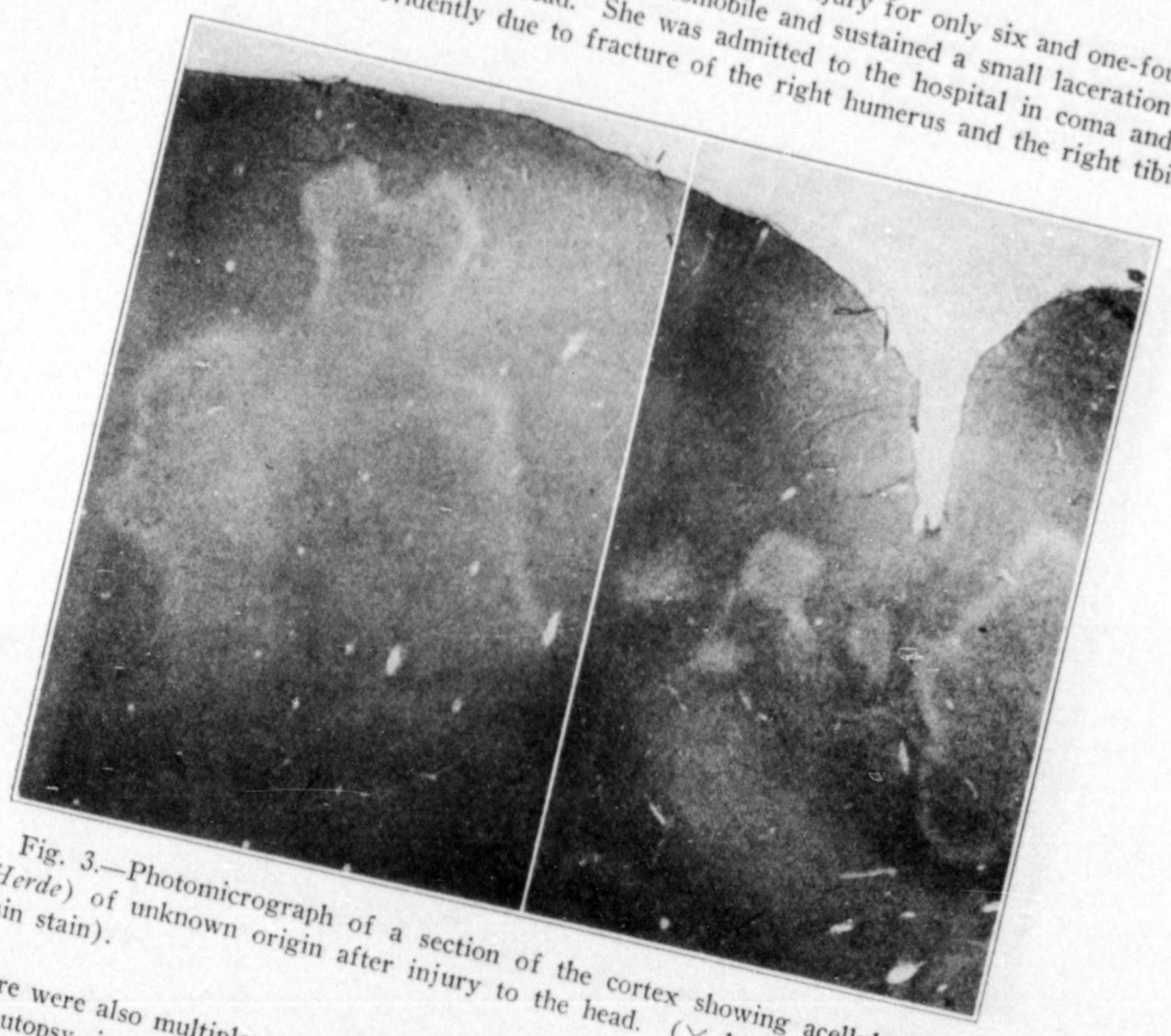

Fig. 3.—Photomicrograph of a section of the cortex showing acellular areas (*Herde*) of unknown origin after injury to the head. (× 14; hematoxylin and eosin stain).

There were also multiple severe lacerations of the abdominal wall and extremities. At autopsy, in addition to the other wounds, generalized severe subdural hemorrhage and a minor subarachnoid hemorrhage, more extensive on the right side, were present. No gross lesions of the brain itself were evident, either externally or internally. On microscopic examination, extensive acellular areas were noted in the cortex of the right temporal and parietal lobes (fig. 3).

The significance of the presence of these areas in the cerebral cortex after injury is not entirely clear. It is evident that they are not a characteristic manifestation of concussion, since they were so rarely observed in our series of cases of injury to the brain. They are, furthermore,

not due to severe cerebral injury, since there was no gross injury to the brain in the case mentioned. They were not universally present but were apparently confined to the right cerebral hemisphere. In discussing the changes of this nature present in the brain in one of their cases, Winkelman and Eckel [4] attributed their presence to edema of the brain, which in turn was due to interference with the blood supply. If these lesions are due to edema they should be observed much more frequently than the results of our special study indicate. It is likely that some additional factor other than the local vascular alteration or the resulting edema must be present to account for their occurrence. In the case of Winkelman and Eckel, as in the case reported in this paper, some degree of shock was present, but more study must be given to the incidence and distribution of lesions of this type after trauma before the etiology can be definitely established.

CORTICAL CONTUSION

Contusion of the cortex may be either a direct or a contrecoup effect of injury. It is probably due to contrecoup in the majority of instances. More rarely it results from a depressed fracture of the cranial vault or base. In this connection we shall limit ourselves to the common contusion of the cerebral cortex, usually due to contrecoup.[5] From an anatomic standpoint one may classify cortical contusions into three essential types: (1) the wedge-shaped contusion, (2) superficial contusion and (3) diffuse contusion. Since the architectural changes in the cortex vary with each type, they will be discussed separately.

Wedge-Shaped Contusion.—Contusion of this type is usually the result of focal injury to the cortex by contrecoup. Its size is dependent on the severity of the injuring force and its location on the direction of force. As a rule it is observed in the subfrontal cortex or in the ventrolateral portion of the temporal cortex. Because of its greater prominence, the ridge of the convolution is predominantly affected. In cross-section the triangular or wedge shape of the injured zone becomes apparent. In the frontal lobe the triangle tends to have a relatively

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4. Winkelman, N. W., and Eckel, John L.: Brain Trauma: Histopathology During the Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934.

5. In this study our primary interest lies in the alteration in the arrangement of the nerve cells of the cerebral cortex. Since, however, when the contusion reaches any magnitude the subcortical white substance is also affected, brief mention will be made of the extension into the subcortex whenever such reference seems germane to the problem at hand.

We have not included other secondary or remote effects of injury to the cortex, such as softening due to vascular occlusion (Courville, C. B., and Olsen, C. W.: Post-Traumatic Cerebral Softening: Delayed Symptoms Suggesting Interval Hemorrhage Following Minor Injury to the Head, West. J. Surg. **43**: 219 [April] 1935).

narrow base, the bruise itself extending deep into the subcortex. On the other hand, in the temporal lobe the outline of this contusion assumes more nearly the shape of an equilateral triangle (fig. 4 *A*).

The essential architectural alterations are dependent on the extent of the original bruise and the amount of hemorrhage. In subfrontal contusion of this type the amount of cortical damage may be small and relatively insignificant. In the temporal lobe, on the other hand, the contusion is relatively more extensive, and large areas of cortex may be destroyed. In minor contusions of this type the affected area is indicated grossly by small shotlike hemorrhages located within the cortex and lying beneath a narrow zone of unaltered cortical tissue. In the

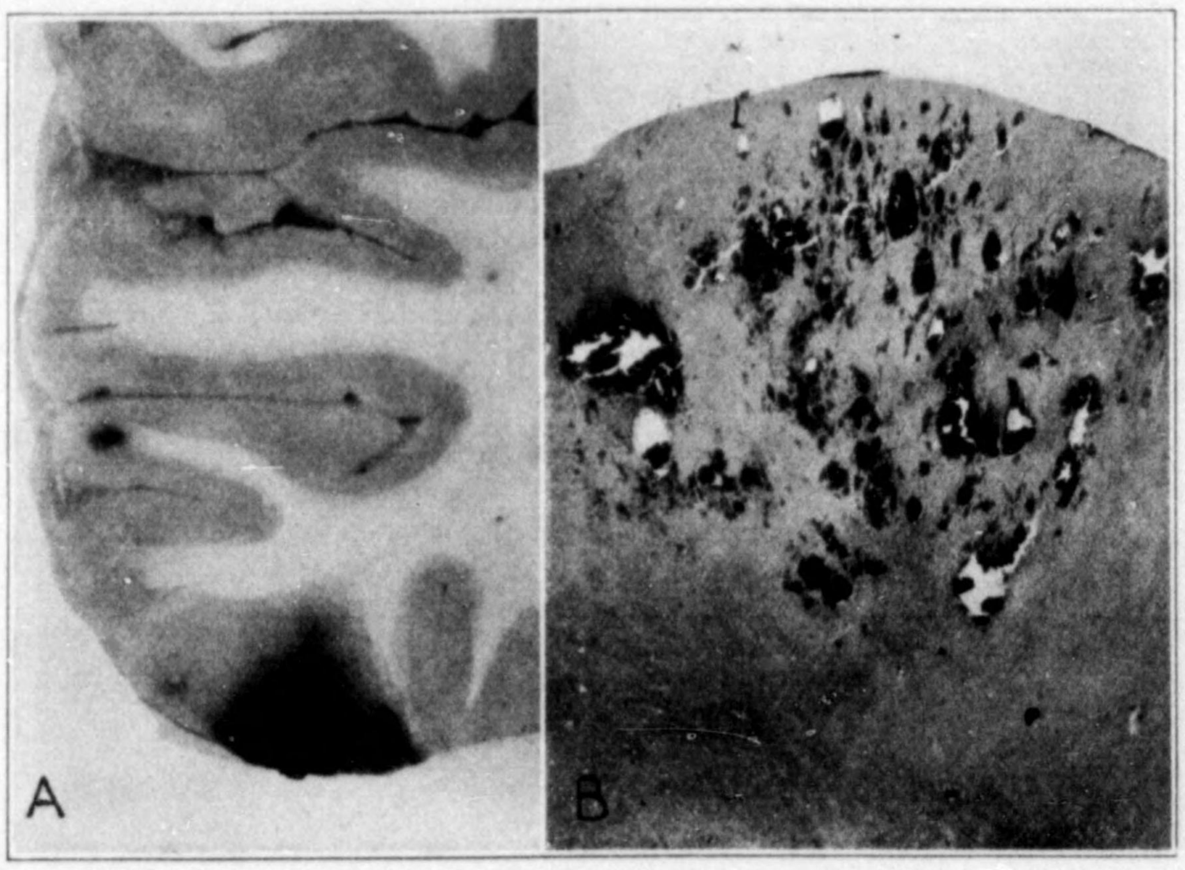

Fig. 4.—(*A*) Photograph showing a small wedge-shaped contusion of the cortex of the third temporal convolution, of about normal size, and (*B*) photomicrograph (× 10; reduced silver method) showing detail of the cortical contusion. Sparing of the subpial glial layer and pallor of the areas of tissue between the hemorrhages are characteristic.

more severe types hemorrhage is more profuse, and the clot approaches the surface, spreads laterally and invades the deeper layers of the cortex. At the margins of a moderately sized contusion there tends to remain an overhang of pia mater and attached subpial cortex, which appears as a hooklike projection on cut section. It may be stated, then, that the type of lesion and the accompanying changes in the cortical architectonics depend essentially on the mechanism of the injury.

In a previous paper in this series [1] the contused area was divided into a number of zones to indicate the reaction of the neuroglia. The

same general plan can be utilized in discussing the effect of injury of this type on nerve cells. There may be considered (1) a central area of immediate destruction, (2) a zone of delayed disintegration and (3) a zone of incomplete injury. The adjoining areas are not permanently injured by the contusion.

Area of Immediate Destruction: In minimal contusion of the cortex this area may consist of one or more separate foci, representing areas of local hemorrhage. The expanding hemorrhage first compresses the adjacent tissue and then destroys it by infiltration and tearing. In a minor injury this process may stop with the formation of several separate and discrete hemorrhages at the point of injury (fig. 4 *B*). In this case the ultimate lesion is characterized by the presence of a number of acellular areas, which, after disintegration and absorption of the red cells, may be confused with the *Verödungs* of different etiology.

In the case of a more severe lesion there is confluence of these foci of expanding hemorrhage, resulting in isolation of intervening bits of cortical tissue, with enclosed nerve cells. These small cortical sequestrums, isolated from their source of nutrition and oxygen, soon disintegrate and become intermingled with the blood clot. Even in cases of contusion only a few hours old, the remnants of these isolated sequestrums are difficult to identify. In still more severe lesions no trace of nerve tissue can be observed from the beginning, and this central zone is represented only by the blood clot which occupies the region.

Zone of Delayed or Secondary Disintegration: In cases of contusion only a few hours old the nerve elements immediately adjacent to the focal hemorrhages show little or no morphologic change in preparations made as a routine. In the preparations impregnated by the method of Ramón y Cajal, these elements show an unusual affinity for reduced silver and appear as dark brown or black outlines in the section.[6] In older lesions evidences of degeneration soon make their appearance in respect to both cellular morphologic characters and structure (figs. 5 *A* and *B*). This process of delayed degeneration occurs in a narrow zone about the area of hemorrhage. With degeneration of the fibrinous and cellular elements of the clot there remains a cavity surrounded by a narrow and somewhat irregular zone in which the process of necrosis is still taking place. If the cavity communicates with the subarachnoid space by rupture of the overlying pia, evacuation of the decadent thrombus is facilitated to a considerable degree.

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6. This phenomenon of preservation necrosis, first described by Ramón y Cajal in experimental wounds of the brain, will be given more attention in our next study concerned with changes in nerve cells. Ramón y Cajal asserted that cells showing this reaction were dead but, because of some property of the blood serum, maintained a strong affinity for reduced silver.

Zone of Incomplete Injury: Adjoining the zone of delayed necrosis is a narrow zone in which injury is less profound and in many cases insufficient to bring about the death of the nerve cell. In dealing with the interstitial elements, this zone has been described as the zone of reversible reaction. This term was used to signify the concept that the cell was not so seriously injured but that recovery might occur. In this zone, however, were observed astrocytes that were morphologically crippled and in which complete recovery was unlikely. These cells, although surviving for some time, probably succumb to regressive

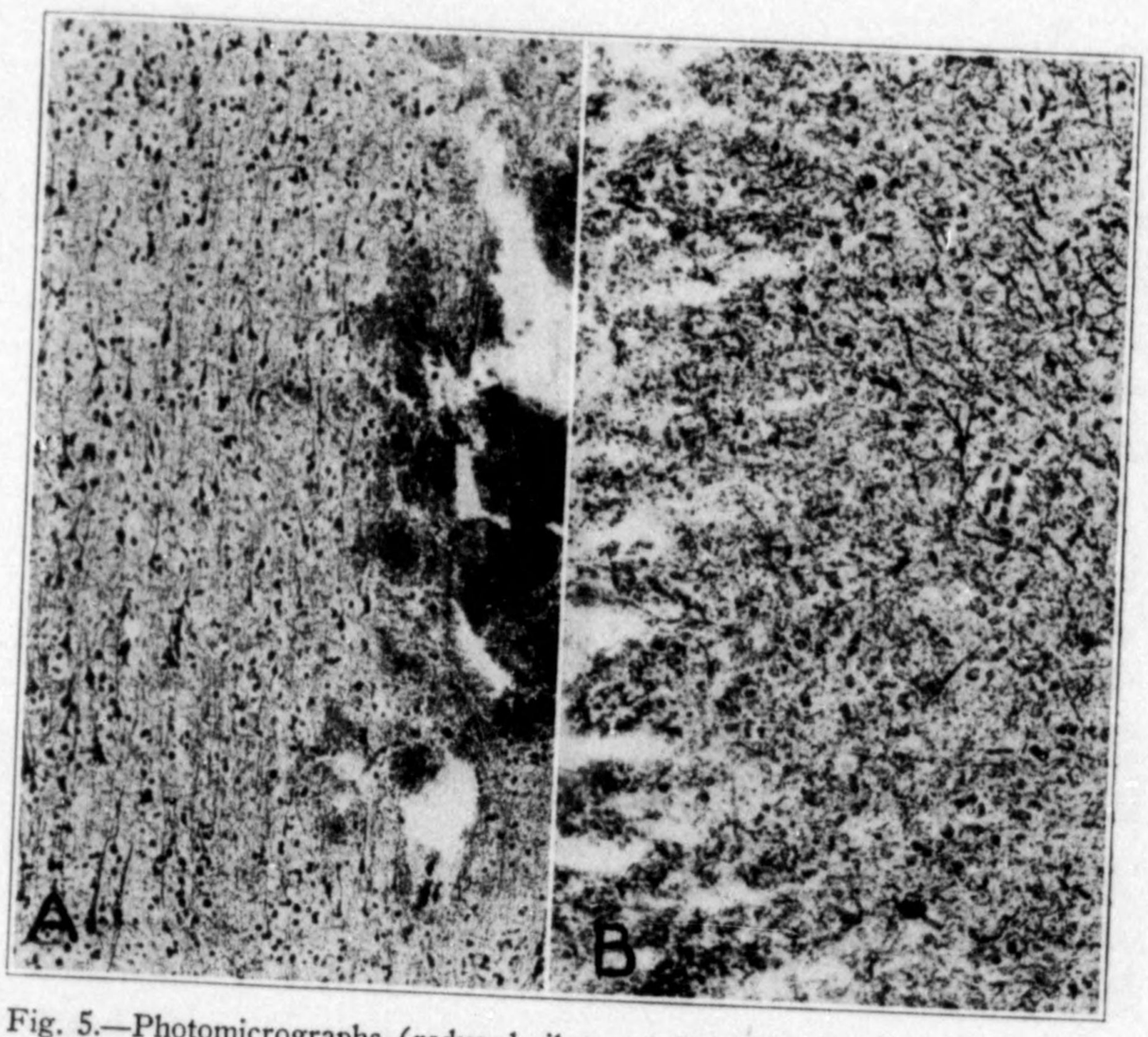

Fig. 5.—Photomicrographs (reduced silver method) showing loss of nerve cells and morphologically altered nerve cells (*A*) in the vicinity of a small cortical hemorrhage (× 80) and (*B*) adjacent to the cortical contusion (× 140).

changes and ultimately disappear. In referring to nerve cells in this zone several possibilities must be considered, although some of them must fall outside the limits of this morphologic study. In this zone, months and even years after injury, crippled nerve cells may be observed, often encrusted with iron.[7] Such cells are probably without function. On the other hand, it may logically be predicated that shortly

7. Courville, Cyril B., and Kimball, T. S.: Histologic Observations in a Case of Old Gunshot Wound of the Brain, Arch. Path. **17**:10 (Jan.) 1934.

after the injury nerve cells in this zone may for the time lose their Nissl substance and undergo changes in the neurofibrillar apparatus and perhaps in other elements of the cytoplasm and nucleus. These cells may sooner or later be capable of regaining incompletely or completely their normal function. These cells may be said to undergo a reversible reaction.

Distal to this third zone the cells undergo no more evident morphologic change than do cells at greater distance from the local injury. In general it may be said that the effect of the injury rapidly decreases

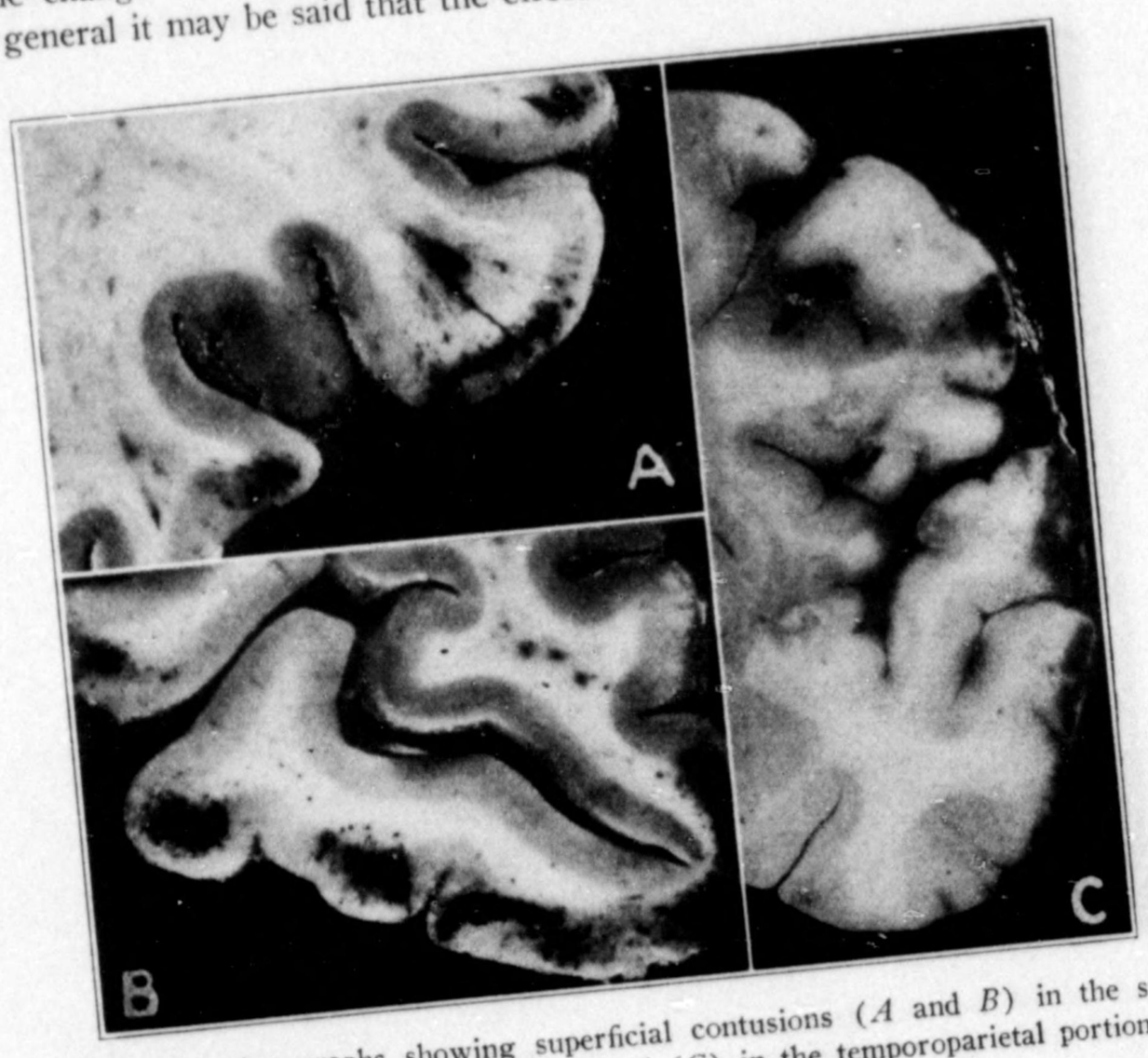

Fig. 6.—Photographs showing superficial contusions (*A* and *B*) in the subfrontal portion of the cortex (× 1⅔) and (*C*) in the temporoparietal portion of the operculum.

as one leaves the margin of the contused area, if the demonstrable morphologic changes in the nerve cells can be taken as a criterion. It is remarkable how close to this margin apparently normal nerve cells can be observed, even after an interval of weeks has passed since the time of injury. This observation lends much weight to the conception that the immediate effect of the original injury is to produce hemorrhage and that this hemorrhage is largely responsible for the extent of cortical damage.

Superficial Contusion.—In contrast to the wedgelike contusion, with its tendency to penetrate the subcortical white substance, is the more widespread superficial and spotlike bruise. It tends to occur where the cortex lies against a gently curving portion of the inner table of the skull, unmarked by convolutional depressions or other irregularities. It may be observed on the basilar surface of the frontal lobe or on either side of the sylvian ridge but is particularly frequent in the opercular and lower portion of the parietal cortex (fig. 6). In these cases severe disintegration of the entire cortex is unusual, even in widespread

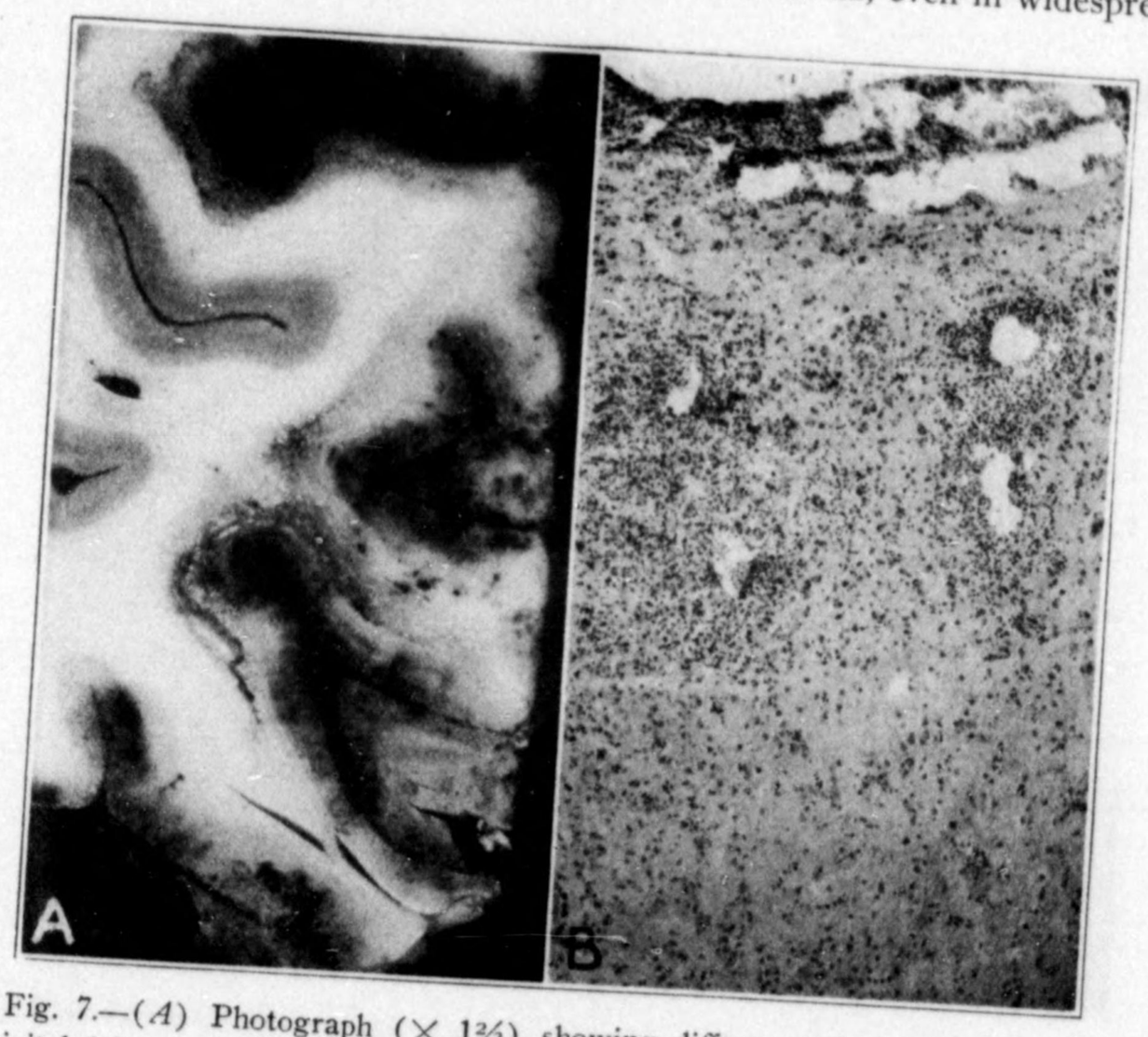

Fig. 7.—(*A*) Photograph (× 1⅔) showing diffuse cortical contusion of the occipital lobe, and (*B*) photomicrograph (× 80; hematoxylin and eosin stain) showing petechial hemorrhage and loss of nerve cells in a diffuse occipital contusion.

lesions. The essential lesion is again a shotlike or streaked hemorrhage, particularly affecting the upper layers of the cortex. In the average case the focal hemorrhages tend to become confluent, giving rise to a mottled or spotty appearance. In the more severe types, but probably not in persons who survive an injury, there occurs at times widespread disintegration of the superficial layers of the cortex. This gives the surface of the brain a "greasy feel" on postmortem examination.

In a lesion of this type the cyto-architectonic change resembles that of minor cortical contusion in other situations. The cells in the immediate region of the enlarging hemorrhage are destroyed. About each separate hemorrhage there occurs a narrow zone of delayed disintegration and reversible change, much more limited in extent than the zone about the larger lesion. The zone about the smaller hemorrhage may not be demonstrable histologically. As the red cells disintegrate, clear local areas remain, which may resemble superficially the *Verödungs* of other etiology. The two lesions should not be confused at this stage. In severe lesions the superficial layers of the cortex at the crest of the convolutions of the affected region may be disintegrated, but, as previously stated, it is unlikely that this occurs in the patient who recovers.

Diffuse Cortical Contusion.—As has been emphasized in another contribution,[8] contusions of the posterior portion of the temporal and the occipital lobe, because of the peculiar anatomic situation, are likely to be diffuse and at times extensive. The arrangement of the cortex is more or less completely disrupted, owing primarily to the large number of focal hemorrhages and secondarily to the impairment of nutrition and tissue respiration incident to the interruption of the blood supply. Large portions of the cortex may undergo complete disintegration in an irregular fashion. In these areas there is more or less complete loss of the nerve cells. These cells soon lose their affinity for stains, and the cortex appears to be devoid of them. Their presence may be demonstrated, however, with the metallic methods. The underlying subcortex is likewise softened and has a yellowish, spotted appearance, due to the occurrence of larger and usually more discrete petechial hemorrhages. Owing to the presumed impairment of circulation, the entire cortex tends to detach itself from the underlying white substance, much as it does in hemorrhagic softening due to venous thrombosis. The essentials of cyto-architectonic change in this lesion are shown in figure 7.

CEREBELLAR CONTUSION

Contusion of the cerebellum is relatively less common. It is usually the result of linear fracture of the occipital bone which runs parallel with the midline, extending into or terminating in the region of the foramen magnum. Rarely it may occur as the result of compound comminuted and depressed fractures of the occipital bone or from forcible contact with the tentorium. It is rarely extensive and seldom affects the subcortex. As a rule the superficial folia are more seriously affected.

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8. Courville, Cyril B.: Diffuse Cortical Contusion of the Occipital Lobe, Arch. Path. **20**:523 (Oct.) 1935.

In cases of minimal contusion of the cerebellum gross examination may show only a few minute foci of hemorrhage and at times nothing. In such instances microscopic sections may show a few infiltrated wandering cells and focal hemorrhage in the molecular layer (fig. 8 *A*). The Purkinje cells may show no changes whatever. As Winkelman and Eckel [4] have indicated, these areas may be multiple. In the more severe conditions the molecular layer may show considerable infiltration with hemorrhage and resultant necrosis of the tissue. When the lesion is even more severe the superficial portion of the folium may be disintegrated so that the layer of Purkinje cells is likewise affected. The contusion extends like a wedge into the underlying cortex, much as it does in the case of contusion of the temporal lobe (fig. 8 *B*).

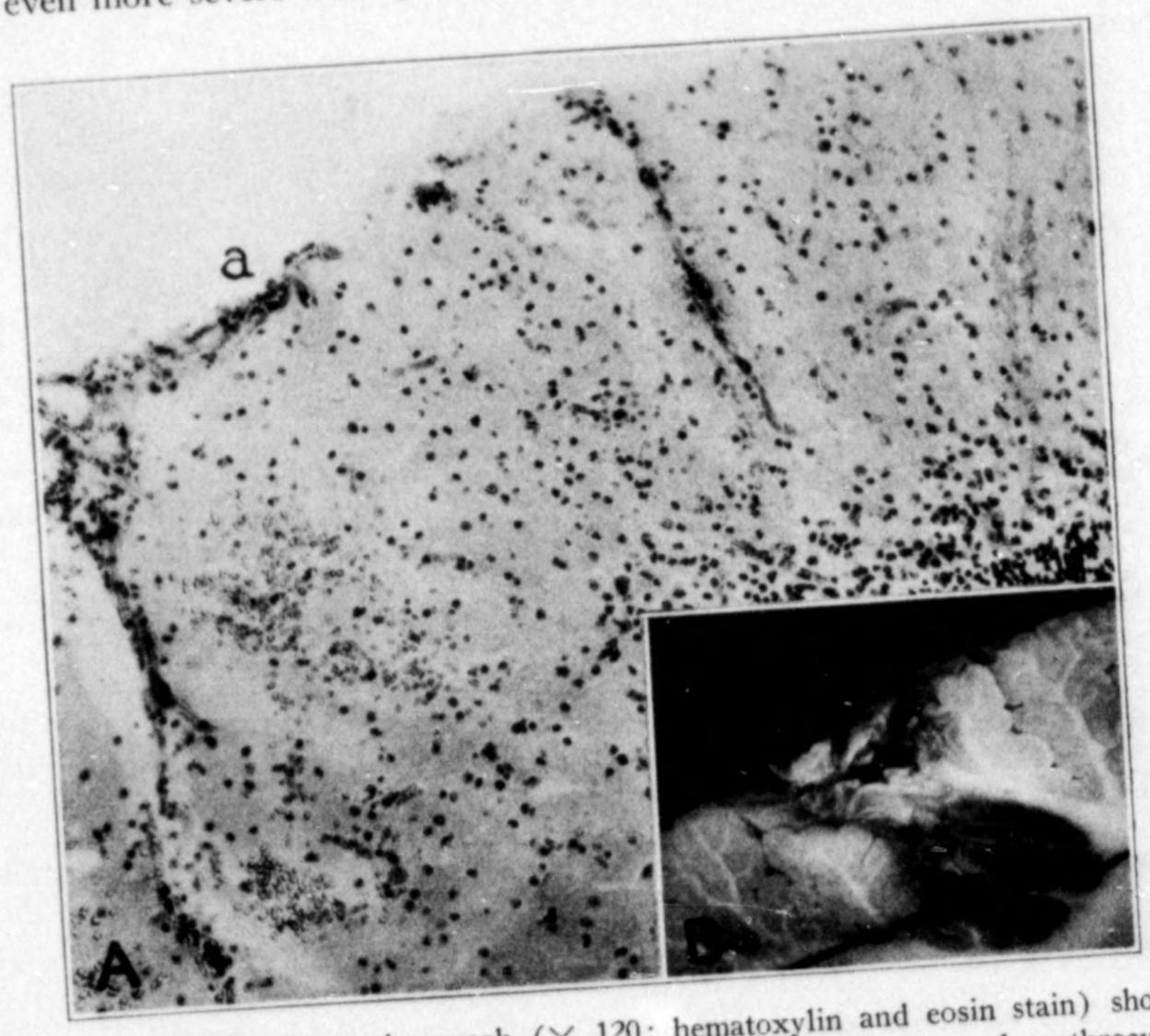

Fig. 8.—(*A*) Photomicrograph (× 120; hematoxylin and eosin stain) showing minimal contusion of the cerebellar cortex. Focal effusions of erythrocytes are shown in the superficial portion of the molecular layer. (*B*) photograph (× 1⅔) indicating superficial foliar contusion and staining of the deeper portions of the cortex, with hemorrhage.

LACERATION OF THE CORTEX

Laceration of the cerebral cortex may be primary or secondary. Primary laceration is due to direct injury of the cortex by an indriven

foreign body or bony fragments. The subcortical white substance is almost invariably injured as well. Secondary laceration is the result of escape of blood to the exterior from an underlying intracerebral hemorrhage. We are not concerned with the second type, even though the hemorrhage which caused it may be of traumatic origin.

So far as the architectural characteristics are concerned, laceration presents certain major points of difference from contusion. These differences suggest the possible alterations which may be observed in the arrangement of the nerve cells in a lesion of this type. The wound

Fig. 9.—Photomicrograph of a section through the margin of an area of contused laceration, showing undermining of the adjacent normal cortex (*C*), × 18; hematoxylin and eosin stain.

is of irregular outline and results in greater destruction of cortical and subcortical tissue than is consequent to contusion. Hemorrhage may be more abundant, since larger cortical vessels may be interrupted. The indriven foreign bodies also aggravate the lesion. The dura is frequently lacerated, and the presence of dural fragments also tends to alter the local tissue reaction.

The essential alterations in cyto-architectonics lie largely in the irregularity of the lesion produced and in the nature of the resulting reaction (fig. 9). The development of the various zones is essentially

the same as in contusion, but the zones show greater irregularity in their margins and variability in width. The more extensive and irregularly distributed foci of hemorrhage, as well as the irregular manner in which the lesion is produced, contribute to the formation of a ragged wound. Groups of nerve cells are likely to be isolated within areas of necrosis. They may be separated from their own and other axons by undercutting of the cortex due to the trauma itself. Such cells are functionally useless, even though they are morphologically sound. These architectural alterations are an early effect and are due to the mechanism by which the wound is produced.

The later architectural changes which are characteristic of severe laceration, with associated injury to the dura, are the result of formation of a scar of connective tissue. It is this type of cortical distortion that has been described by Foerster and Penfield[9] as a result of war wounds of the brain and which they asserted is responsible for the epileptiform attacks which occur frequently in such instances. By the gradual contraction of the scar the adjacent cortex is pulled toward the site of the original wound. The astrocytes tend to assume a radiating arrangement, pointing toward the center of the scar. We have had the opportunity to study but one case of this type; in this instance the time interval was not sufficient to permit the development of a strong scar of connective tissue. A lesion of this type is exceptional after traffic accidents.

SUMMARY AND CONCLUSIONS

Alterations in nerve cells following trauma to the head include: (1) disturbance in their normal arrangement and (2) changes in their structure. Since problems concerning each of these phases differ so widely, only the first has been considered in this paper. Alterations in nerve cells will be the subject of a forthcoming study.

Cyto-architectonic alterations due to cortical contusion and laceration were studied in 39 cases. A study of focal necrosis was made in an additional series of 18 cases. Various details of contusion have been studied in a total of 229 cases.

In the areas of cortical necrosis (*Herde, Verödungs*) the changes are probably due to deprivation of oxygen, although the exact mechanism of their production is not known. The lowering of the blood pressure incident to shock may be a contributing factor.

In contusion of the brain the force of the blow is responsible for hemorrhage into the cortex as well as for the bruise itself. Hemorrhage is responsible to a great extent for the architectural alterations resulting from such a lesion.

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9. Foerster, O., and Penfield, W.: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

Nerve cells are able to maintain their morphologic identity remarkably near the margin of a contusion. Crippled nerve cells may be present in partially disorganized areas for months and years after the injury.

Three zones of action are to be observed in the injured cortex: (1) a zone of immediate and complete destruction of nerve elements, (2) a zone of delayed disintegration and (3) a zone of incomplete and at times recoverable injury. In the last zone nerve cells which may be morphologically crippled may survive for years. Other cells, more distantly removed, may undergo certain minor structural changes capable of complete recovery.

Cyto-architectonic changes resulting from laceration of the cortex may be considered as primary, or early, and secondary, or late. The primary changes, due to the immediate effect of the traumatizing agent, are characterized by irregular contour of the areas of degeneration and variable width of the marginal zones. The late alterations, resulting from the pull of the scar on the adjacent cortex, are of variable degree, dependent on the amount of connective tissue and the extent of its adhesion to the dura.

Histologic Studies of the Brain in Cases of Fatal Injury to the Head

IV. REACTION OF THE CLASSIC NEUROGLIA

CARL W. RAND, M.D.
AND
CYRIL B. COURVILLE, M.D.
LOS ANGELES

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The cerebral states following acute injuries to the brain, particularly those included under the elusive term of concussion, have long been the subject of considerable conjecture. A satisfactory physiologic and pathologic explanation for the acute or chronic clinical symptoms manifested has not been clearly established. For example, the individual nervous and mental phenomena that so frequently appear as an aftermath to brain injury have been attributed by some to generalized gliosis or to other diffuse tissue change. To the contrary, there are others who believe that such manifestations are to be explained largely on a functional basis. Is the solution of the problem to be sought in histologic studies? Can sufficient alterations be found in the various cellular elements to account for immediate as well as remote symptoms? What alterations take place in these cells, and what is their significance? In what measure can the reaction of the classic neuroglia be taken as an index of disordered nerve function? These and many other questions arise and demand an answer. As far as we are able to determine, a thorough study of the finer changes in the constituent elements of the nervous system has not been made in cases of injury of the human brain. In this contribution, the fourth of a series of studies,[1] we are concerned with the reaction of the classic neuroglia.

REVIEW OF THE LITERATURE

It is not our purpose to discuss in detail the history of the supporting elements of the central nervous system, as this has been so ably accomplished by others. Since Virchow[2] established the identity of

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From the Neurological Service and the Neuropathological Laboratory of the Los Angeles County General Hospital.

1. Rand, C. W.: Histologic Changes in the Brain in Cases of Fatal Injury to the Head: I. Preliminary Report, Arch. Surg. **22**:738 (May) 1931. Rand, C. W., and Courville, C. B.: II. Changes in the Choroid Plexus and Ependyma, ibid. **23**:357 (Sept.) 1931; III. Reaction of Microglia and Oligodendroglia, Arch. Neurol. & Psychiat. **27**:605 (March) 1932.

2. Virchow, R.: Ueber das granulierte Ansehen der Wandungen der Gehirnventrikel, Allg. Ztschr. f. Psychiat. **3**:242, 1846.

cells which constitute the supporting framework of the functional elements, certain definite lines of investigation have been followed. Their histologic character was shown by Golgi,[3] who first demonstrated cellular detail with his silver impregnations, by Weigert,[4] whose staining method demonstrated glia fibrillae, and finally by Cajal,[5] whose gold sublimate method established their absolute identity. The question of a syncytium, first illustrated but not described by Frommann,[6] elaborated more fully by Held[7] and Hardesty,[8] and finally discounted as an artefact of staining by Achucarro,[9] is now of little moment. From the standpoint of classification, the "mossy" and "spider" cells of Golgi were soon described as protoplasmic and fiber cells by Kölliker[10] and Andriezen.[11] In addition to the classic neuroglia, it was soon recognized that some of the interstitial elements could not be demonstrated by any of the existing methods. These have since been recognized as mesodermal (microglia) as well as ectodermal (oligodendroglia) in origin. To these basic studies have been added innumerable other contributions on staining methods, on minute details of their structure, and particularly on their alteration in various pathologic lesions of the central nervous system. Of the latter we have chosen to review only those dealing with the changes in the classic neuroglia following traumatic lesions.

LITERATURE ON NEUROGLIAL CHANGE FOLLOWING EXPERIMENTAL INJURY

In reviewing the literature dealing with neuroglial changes consequent to injury, the following aspects of experimental injury have been

3. Golgi, C.: Sulla fina anatomia della sistemo nervoso, Milan, U. Hoepli, 1886.

4. Weigert, C.: Beiträge zur Kenntnis der normalen menschlichen Neuroglia, Frankfurt, August Weisbrod, 1895.

5. Ramón y Cajal, S.: Sobre un nuevo proceder de impregnacion de la neuroglia y sus resultados en los centros nerviosos del hombre y animales, Trab. d. lab. de invest. biol. Univ. de Madrid **11**:219, 1913.

6. Frommann, C.: Untersuchungen über die normale und pathologische Histologie des centralen Nervensystems, Vienna, Friedrich Frommann, 1876.

7. Held, H.: Ueber den Bau der Neuroglia und über die Wand der Lymphgefässe in Haut und Schleimhaut, Abhandl. d. math.-phys. Kl. d. k. sächs. Gesellsch. d. Wissensch. **28**:199, 1904.

8. Hardesty, Irving: On the Development and Nature of the Neuroglia, Am. J. Anat. **3**:229, 1904.

9. Achucarro, N.: Notas sobre la estructura y functiones de la neuroglia y en particular de la neuroglia de la corteza cerebral humana, Trab. d. lab. de invest. de biol. Univ. de Madrid **11**:186, 1913.

10. Kölliker, A. v.: Handbuch der Gewebelehre des Menschen, ed. 2, Leipzig, W. Engelmann, 1893.

11. Andriezen, W.: The Neuroglia Elements in the Human Brain, Brit. M. J **2**:227, 1893.

considered: (1) simple puncture wounds, with or without removal of central core, (2) simple linear incisions, (3) extensive brain wounds, (4) embedded foreign bodies and (5) traumatic brain hemorrhage.

Simple Puncture Wounds.—Coen [12] and Tschistowitsch [13] were evidently the first to study experimental puncture wounds of the brain. The latter studied wounds made in the brain of pigeons and dogs with platinum needles, and the cellular reaction which followed from three to one hundred days after injury was noted. He concluded that the connective tissue elements from the pia mater and blood vessels played the chief rôle in the resulting scar. The neuroglia, in his opinion, had to do only with the formation of a narrow zone of sclerosis and the consequent shrinkage of the scar.

Very little experimental work was done after the investigations of Tschistowitsch until Penfield [14] and Penfield and Buckley [15] studied neuroglial changes following both blunt needle and trocar punctures. Where the damaged brain tissue was left in situ, there was a hypertrophy of the regional astrocytes, and the protoplasmic forms were transformed into the fibrous type. The cells assumed a concentric arrangement about the needle tract, with their larger expansions radiating from it, owing to the contraction of the connective tissue core. When the central core was removed by a hollow trocar, there was a minimal amount of connective tissue formation, with only a minor degree of glial reaction in the gray matter and practically none in the white matter. Del Rio Hortega and Penfield [16] described two types of neuroglial change about experimental brain punctures. The first, in which the cells were undergoing destruction, was characterized by coarse granulation of the cytoplasm and pigmentation of the expansions. The second, leading to typical glial proliferation, was manifested by a swelling of the cell body and fine granulation of the cytoplasm. This stage led to typical direct cell division and to the transformation

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12. Coen, E.: Ueber die Heilung von Stickwunden des Gehirns, Beitr. z. Physiol. **2**:107, 1887.

13. Tschistowitsch, T.: Ueber die Heilung aseptischer traumatischer Gehirnverletzungen, Beitr. z. path. Anat. u. z. allg. Path. **23**:321, 1898.

14. Penfield, Wilder: Meningocerebral Adhesions: A Histological Study of the Results of Cerebral Incision and Cranioplasty, Surg., Gynec. & Obst. **39**:803, 1924; The Mechanism of Cicatricial Contraction in the Brain, Brain **50**:499, 1927.

15. Penfield, W., and Buckley, R. C.: Punctures of the Brain: The Factors Concerned in Gliosis and in Cicatricial Contraction, Arch. Neurol. & Psychiat. **20**:1 (July) 1928.

16. del Rio Hortega, P., and Penfield, W.: Cerebral Cicatrix: The Reaction of Neuroglia and Microglia to Brain Wounds, Bull. Johns Hopkins Hosp. **41**:278, 1927.

from protoplasmic into fibrillary astrocytes. Linell [17] repeated the work of Penfield and his associates and confirmed their observations. He believed that the maximum neuroglial reaction, the purpose of which was to form a barrier between normal and damaged brain tissue, was reached at the end of three weeks.

Practically all investigators are in accord as to the sequence of changes produced when the brain is punctured with a blunt needle. In a narrow degenerative zone about the puncture wound the cellular elements, including the neuroglia as well as the nerve fibers themselves, undergo regressive changes. The débris is subsequently phagocytosed by the developing compound granular corpuscles. Beyond this is a zone in which the glia cells hypertrophy and proliferate, leading to formation of a paracentral gliosis. The absence of connective tissue proliferation and gliosis following the removal of the central core by a hollow needle suggested that the degenerating brain tissue, if left in the tract, is the exciting cause of such reaction.

Pfeifer [18] was probably the first to study the changes in the human brain following needle puncture in an operative attempt to localize cerebral tumors. He concluded that neuroglia played no part in the repair of such wounds, the scar being formed solely by connective tissue. Wilson [19] studied the neuroglial reaction in one case in which ventricular puncture was done six days before death, and another in which six punctures were made from seven to eleven and a half months before death. In the first case he described a central zone of intense cellular reaction, and a more distal zone containing hypertrophied astrocytes. In the second case, in which the wounds were older, similar conditions were present, except that the connective tissue reaction was well advanced while the neurogiial response was less acute. Cone [20] studied the neuroglial reaction to a ventricular puncture made ten days before death. He referred only to the regressive changes taking place in the astrocytes. In a general way we have been able to confirm their observations in studying the tract of a needle puncture made three and a half months before death.

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17. Linell, Eric A.: The Histology of Neuroglial Changes Following Cerebral Trauma: An Experimental Investigation, Arch. Neurol. & Psychiat. **22**:926 (Nov.) 1929.

18. Pfeifer, B.: Zur Diagnose von Hirntumoren durch Hirnpunktion, Jahrb. f. Psychiat. u. Neurol. **28**:323, 1907; Fortschr. d. Med. **27**:24, 1909.

19. Wilson, R. B.: Brain Repair, Arch. Neurol. & Psychiat. **15**:75 (Jan.) 1926.

20. Cone, William: Acute Pathologic Changes in Neuroglia and Microglia, Arch. Neurol. & Psychiat. **20**:34 (July) 1928.

Simple Linear Incision.—It seems strange that simple incisions of the brain have not been given more attention than a study of the literature would seem to indicate. Cajal [21] described the neuroglial reaction following simple linear wounds in which no large vessels had been damaged. In these the neuroglia had a radial and tangential arrangement similar to that described about puncture wounds. There was but a minor connective tissue core. The individual astrocytes stained less intensely with gold sublimate, and granulation of the processes occurred, usually first appearing in the sucker foot. Regressive changes of more marked degree took place in the cells immediately adjacent to the wound with the formation of ameboid glia. In other words, simple radial incisions of the cortex with a sharp knife produce changes similar to puncture wounds, resulting in a plane of reaction rather than one about a central core. The small amount of connective tissue present in the wound was probably due to the absence of extensive tissue damage or hemorrhage. The rather active proliferation of glia in the absence of connective tissue suggests the possibility that one is not dependent on the other.

Extensive Brain Wounds. — In addition to simple linear wounds, Cajal also studied extensive ones with contusion and serious hemorrhage. He found that cicatrization resulted largely from mesodermal proliferation and increased vascularization. Outside of the connective tissue scar was a zone of gliosis of varying thickness. The changes in the regional astrocytes appeared to be identical with those of the more simple brain wound. Of especial interest, and a point to which we will call attention later, was the rôle that gross hemorrhage played in the formation of the resultant scar. With a moderate or extensive hemorrhage, liquefaction and phagocytosis of the blood cells outstripped the reparative reaction, and a cyst resulted. The marginal zone of softening came to be occupied with large numbers of compound granular corpuscles. The process of cyst formation seems to limit mesodermal reaction to a narrow zone forming the cyst wall.

Effect of Foreign Bodies.—The healing of brain wounds is often complicated by the presence of foreign bodies. These may compress the brain, as occurs in simple depressed skull fractures, or dislocated bone fragments or other foreign material may be embedded within the brain substance. As we will show in a later section, hemorrhage into the brain substance for all practical purposes acts as a foreign body and influences in a special way the reparative process. In this connection we will summarize the contributions dealing with the neuroglial reaction to experimentally placed foreign bodies either on the surface or embedded within the brain substance.

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21. Ramón y Cajal, S.: Degeneration and Regeneration of the Nervous System, London, Oxford University Press, 1928, vol. 2, p. 727.

Foreign Bodies Placed Outside of the Brain: Penfield found that when a nonirritating substance, such as celluloid, was placed over an intact brain, there was no evidence of a diffuse reaction of the neuroglia except perhaps at its margin where some thickening of the superficial glial layer took place. In this case the reaction to the foreign body was essentially mesodermal. In a series of experimental depressed fractures of the skull with foreign bodies introduced into the extradural space, Naffziger and Glaser [22] found no regional gliosis. This only occurred when the brain itself had been damaged by the force of the blow which produced the fracture. This would lead one to believe that the foreign body itself, carefully placed so as to compress the surface of the brain, is incapable of producing a regional gliosis.

Foreign Bodies Within the Brain: Borst [23] studied the reaction of the brain following the introduction of celloidin blocks into the cortex of rabbits. He believed that the neuroglial elements invaded the foreign body itself, an observation which subsequent investigators have failed to confirm. Farrar,[24] in studying the changes following the introduction of sterile elder marrow into the cortex of rabbits, found that the resultant reaction could be divided into: (*a*) an initial passive period for the first twenty-four hours, (*b*) a subsequent period of proliferation and (*c*) a terminal period, characterized by involutional changes. The first period was characterized by a thickening of the overlying pial membrane with the formation of fibroblasts and phagocytic cells. Only minor regressive changes were found in the cortical elements. The second stage was characterized by a gradual replacement of the hematogenous elements in the foreign body by fibroblasts, the formation of a connective tissue sheath and the gradual phagocytosis of the zone of softened brain tissue. Outside the latter zone, reactive gliosis occurred. The terminal stage of the condition was a complete replacement of the foreign body by mesodermal elements, associated with a surrounding zone of connective tissue. A zone of reactive gliosis finally surrounded the entire mesodermal mass. These observations were confirmed by Morgenthaler,[25] who noted a connective tissue zone separating the regional gliosis from the foreign body.

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22. Naffziger, H. C., and Glaser, M. A.: An Experimental Study of the Effects of Depressed Fractures of the Skull, Surg., Gynec. & Obst. **51**:17, 1930.

23. Borst, M.: Neue Experimente zur Frage nach der Regenerationsfähigkeit des Gehirns, Beitr. z. path. Anat. u. z. allg. Path. **36**:1, 1904.

24. Farrar, C. B.: On the Phenomena of Repair in the Cerebral Cortex: A Study of Mesodermal and Ectodermal Activities Following the Introduction of a Foreign Body, Histol. u. histopath. Arb. ü. die Grosshirnrinde **2**:1, 1908.

25. Morgenthaler, W.: Heilungsvorgänge in der Grosshirnrinde des normalen und alkoholisierten Kaninchens nach Einführung eines Fremdkörpers, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:431, 1912.

MATERIAL AND METHODS

The material used in this study was forwarded to us by Dr. A. F. Wagner and Dr. J. H. Schaefer of the coroner's department. All the cases that have been studied clinically have come under our observation. A few of the persons who succumbed within a short time or were killed outright were taken directly to the coroner's morgue. The cases in this series are practically the same as those studied in our previous contribution on the reaction of microglia and oligodendroglia.

Blocks of tissue were taken from selected areas of the brain and were stained by the following methods: hematoxylin and eosin, scharlach R, Mallory's phosphotungstic acid-hematoxylin, aniline blue, silver carbonate method for neuroglia and Cajal's gold sublimate method. While we have selected blocks of tissue primarily from the standpoint of local injury, we have also taken them on occasion from the cortex and underlying white matter at points distant from any gross injury. Our purpose in this has been to observe any possible distant effects of the injury on the astrocytes. We have grouped the various cases from the standpoint of the type of lesion in order to trace the various stages of neuroglial reaction.

NORMAL NEUROGLIA

Astrocytes are classified as fibrous and protoplasmic. In addition, there are individual cells that seem to have characteristics of both. Protoplasmic astrocytes, the normal habitat of which is the gray substance, elaborate no fibrils, and their rather complex branches form an arborization about the cell body. The fibrous astrocytes, on the contrary, have longer and less ramified expansions consisting of fibrils which pass through the cell body. They are found in the white substance and in the subpial layer. In either type one or more large expansions form an attachment to regional blood vessels. The function of these "sucker feet" is now believed to be that of support rather than of nutrition. The cell bodies of both types are about equal in size, and when demonstrated, with either a stain or a metal, have a granular appearance. In degenerative conditions it is an alteration in these probable lipoidal granules that results in the formation of neutral fat. We shall have occasion to refer to changes in these cytoplasmic granules later. Centrosomes are also found, usually at the point of attachment of the sucker foot. The Golgi apparatus has not been demonstrated in adult neuroglia. Coarser round or oval granules, known as gliosomes, occur both in the cytoplasm of the cell body and along the processes. Their eccentric situation in the expansions can probably be accounted for by the presence of fibrils in these structures. Some observers conclude that the gliosomes are of the nature of mitochondria and are responsible for the formation of the fibrils themselves. Del Rio Hortega, to the contrary, believes that this is not the case. The glia fibrils, evidently an integral part of the fibrous astrocyte, apparently serve as strong binding elements for bundles of nerve fibers.

They are also present in the sucker foot, and thereby come into contact with the regional blood vessel. This serves to strengthen their vascular attachment.

The nuclei are round or oval and have a well defined membrane. The chromatin substance is found as finely divided granules. The larger granules usually present in the central portion of the nucleus under certain circumstances become adherent to the nuclear membrane. In the hematoxylin and eosin stain the larger granules are dark purple, while finer, dustlike granules have a pinkish tint. It has been of interest to trace changes in these various structures following injuries.

CHANGES IN NEUROGLIA FOLLOWING INJURY

As has already been intimated in previous studies of this series, the various cellular elements have shown a specific local or general reaction to injury. The reaction of each element depends on its specific function. Previous investigators have shown that the neuroglia undergoes three distinct types of change in the neighborhood of experimentally traumatized brain tissue: (1) regressive changes leading to complete destruction, (2) hypertrophy and direct cell division of more remotely situated astrocytes and (3) a reversible reaction in an intermediate zone in which moderately altered glia cells may be restored to functionally active ones. There are structurally three distinct zones in the region of damaged brain tissue, to which another may be added when the nature of the reactive change is fully appreciated. In the first zone the various elements are damaged beyond recognition, resulting in a more or less homogeneous débris. An immediately adjacent zone of variable width, depending on the degree of injury, is composed of cellular elements and nerve fibers which are doomed to complete destruction. While these are histologically recognizable immediately following the injury, regressive changes soon occur which lead to complete disintegration of the involved structures. Therefore, in the two zones just described, the end-result is probably the same for all types of cells and fibers regardless of their nature or function.

In the third zone, or zone of reaction, the changes occurring in the various individual elements depend on the specific function of each. In this connection we shall confine ourselves to the changes occurring in the neuroglia. From a functional standpoint this zone may be subdivided into two parts. In a rather narrow strip bordering the zone in which all elements are degenerating, the astrocytes undergo a degree of regressive change from which they are capable of recovering. Penfield has aptly termed this process a reversible reaction. The second part of this zone, considerably wider than the first, is characterized by a positive reparative reaction in the neuroglia, manifested by hyper-

trophy and proliferation. These zones are by no means clearcut, particularly in the jagged and irregular contusions and lacerations of the human brain. This situation is also probably influenced by the susceptibility of individual cells, as it is not uncommon to find one or more of them in a restricted area undergoing complete destruction while their adjacent fellows appear to be unaffected.

It is to the first subdivision of the third zone, where reversible reaction occurs, that we wish to direct especial attention in this study. Our observations will be discussed more in detail in later paragraphs.

THE REACTION OF NEUROGLIA TO SPECIFIC TYPES OF BRAIN INJURY

At the risk of appearing to be somewhat didactic, we have chosen to consider changes in the classic neuroglia which follow specific injuries to the brain. Its practicability to the clinical observer is evident, for it is of importance to understand the pathologic changes and ultimate outcome of a given lesion if only from a prognostic standpoint. Furthermore, this information forms a basis for future operative therapy, as has already been emphasized by Foerster and Penfield.[26] By following this plan it will be much easier to compare the various types of experimental injury, from the standpoint of neuroglial change, with those occurring in the human brain.

This problem following head injury will be considered under two headings: (*a*) the neuroglial reaction to specific traumatic lesions, and (*b*) the peculiar changes occurring in the astrocytes in such injuries. The following varieties of injury will be considered: (1) minor cortical contusion; (2) severe cortical and subcortical contusion with hemorrhage; (3) laceration; (4) hemorrhage, both gross and microscopic, and (5) incidental lesions such as local infarctions following fat embolism. In the accompanying table our cases have been classified from the standpoint of gross pathology on the basis of the lesions just enumerated.

Minor Cortical Contusions.—We have chosen to consider minor cortical contusions apart from more extensive ones, as such lesions are probably present in many persons surviving an injury. They are characterized by a discoloration of the cortex alone, with a nominal amount of hemorrhage. The bleeding occurs either as localized petechial hemorrhages, or as rows of blood cells between nerve fibers radiating toward the cortex. Within the involved area of even minor bruising the astrocytes showed an early tendency to fragmentation of their processes, and their cell bodies in some cases were filled with vacuoles (case 13,

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26. Foerster, O., and Penfield, W.: The Structural Basis of Traumatic Epilepsy and Results of Radical Operation, Brain **53**:99, 1930.

survival period two hours). The cell boundaries were very irregular and the nuclei were small and eccentric. No evidence of direct cell division was observed. In another case (case 6, the patient living about four days after the injury), active direct cell division was taking place at the margin of the bruised area and in the subcortical white matter, with hypertrophy of the reacting cells. The cells in the involved area and about local petechial hemorrhages were undergoing regressive

Classification of Gross Traumatic Lesions

Case	Age	Sex	Survival Period	Gross Lesions
				Cortical Contusions—Minor
13	10	M	2 hours	Contusion base of both frontal lobes
6	26	M	3 days, 19 hours	Minor contusion left frontal lobe
9	32	M	14 days	Contusion left frontal lobe
				Cortical Contusions—Severe
19	70	F	Killed outright	Contusion right temporal lobe
1	63	F	¾ hour	Contusion left temporal lobe with petechial hemorrhages
17	84	F	1¼ hours	Contusion basilar surface both frontal lobes
14	75	F	2 hours	Contusion right frontal and right temporal lobes
3	41	M	2 hours	Contusion anterior poles both frontal lobes
5	38	M	6¾ hours	Contusion cortex right temporal lobe
23	30	M	12 hours	Contusion left temporal lobe
11	9	F	26 hours	Extensive contusion left temporal lobe
21	17	F	56 hours	Contusion right and left temporal and right frontal lobes
6	26	M	3 days, 19 hours	Contusion cortex left temporal lobe
25	38	M	21 days	Contusion right temporal lobe
				Laceration
14	75	F	2 hours	Laceration right frontal lobe
7	14	M	38 days	Severe laceration left temporoparietal region
				Hemorrhage—Gross
2	29	M	31 hours	Hemorrhage into left temporal lobe
4	51	M	7 months	Old gross hemorrhage right temporal lobe
20	48	M	5 days	Gross hemorrhage into left temporal lobe
				Hemorrhage—Petechial
19	70	F	Killed outright	Widespread petechial hemorrhages
10	35	M	14 hours	Multiple petechial hemorrhages left cerebral hemisphere
18	35	M	3 days, 3 hours	Generalized petechial hemorrhages
16	67	M	3½ days	Petechial hemorrhages both frontal lobes
6	26	M	3 days, 19 hours	Petechial hemorrhages white matter left frontal lobe
8	22	M	4½ days	Multiple widespread petechial hemorrhages
22	38	M	6½ days	Widespread petechial hemorrhages
4	51	M	7 months	Petechial hemorrhages adjacent to major hemorrhage

change. It was of interest to note that the degree of activity of direct cell division was in inverse proportion to the proximity to the injury. Some very interesting changes were found in the brain of a person (case 9) surviving a minor bruise for fourteen days and succumbing to a complication. Within the central portion of the bruised area, "ghost" forms of ameboid glia were present just outside a zone of phagocytosis. In the zone just outside that in which active destruction was taking place, a peculiar reaction of the neuroglia was observed. Peculiar unipolar and bipolar cells were observed which appeared to be the result of a loss of several cell processes. These cells, suggestive

of "embryonic cells" observed in gliomas, appeared to be well impregnated with gold, as though they were still living forms. Another observation worth mentioning was the overtaking of local double forms by regressive change. In such instances one of the two cells often appeared to be undergoing regressive change with loss of its processes, while the other appeared to be viable. The degree of cellular proliferation was again found to be inversely proportional to the distance from the injured area, being very active in the adjacent zone and becoming less so deeper in the white substance.

While none of our cases showing minor bruising have been followed for more than two weeks, one can anticipate fairly accurately what the end-result will be. The occurrence of phagocytosis in the central portion and the active peripheral glial reaction suggest that the final condition will be a small patch of gliosis with a degree of contraction, which probably does not involve the arachnoid. Small local or regional petechial hemorrhages will probably result in the formation of small cystlike cavities lined with connective tissue and filled with xanthochromic fluid. This particular detail will be discussed later.

Severe Cortical and Subcortical Contusions with Hemorrhage.—It has seemed best to classify cortical contusions as minor and severe, the essential difference being in the size of the bruised area and the additional factor of gross hemorrhage. This factor of gross hemorrhage plays an important rôle in the production of the terminal picture. As the neuroglial changes accompanying hemorrhage are to be described under a separate heading, we shall confine ourselves to a description of these changes in the bruised area. We have included in this heading of severe contusion those cases in which the cortex and subcortical tissue were involved and marked by hemorrhages larger than the usual petechial extravasation. In many of them there was a clot of variable size which had actually replaced the cortical tissue, around which additional smaller satellite hemorrhages were found. Histologically, the lesion was characterized by a breaking up of extensive areas of cortex marked by large hemorrhagic extravasions.

In a rather characteristic manner the changes in the neuroglia might be classified into three types depending on the zone in which the cell chanced to be found. This is in accord with the observations of Penfield and others. The first zone is a rather narrow one found immediately adjacent to the large central or smaller peripheral hemorrhages, and characterized by an almost immediate and total destruction of the astrocytes. It is difficult even in recent cases to demonstrate the remains of such cells in the markedly altered débris. This zone may be made to include the adjacent tissue in which the neuroglia undergoes regressive change leading to complete destruction within the next few days. We have grouped these two zones as *the zone of complete*

regressive change. One may trace in the peripheral portion of this zone typical acute degeneration of the neuroglia, the details of which will be described in later sections. These zones are indicated in figure 1.

A mesial zone may be designated as *the zone of reversible reaction,* which overlaps to some extent the bordering areas on either side. The difficulties in sharply outlining this zone are apparent when it is realized that it is impossible to tell when looking at a cell in any given

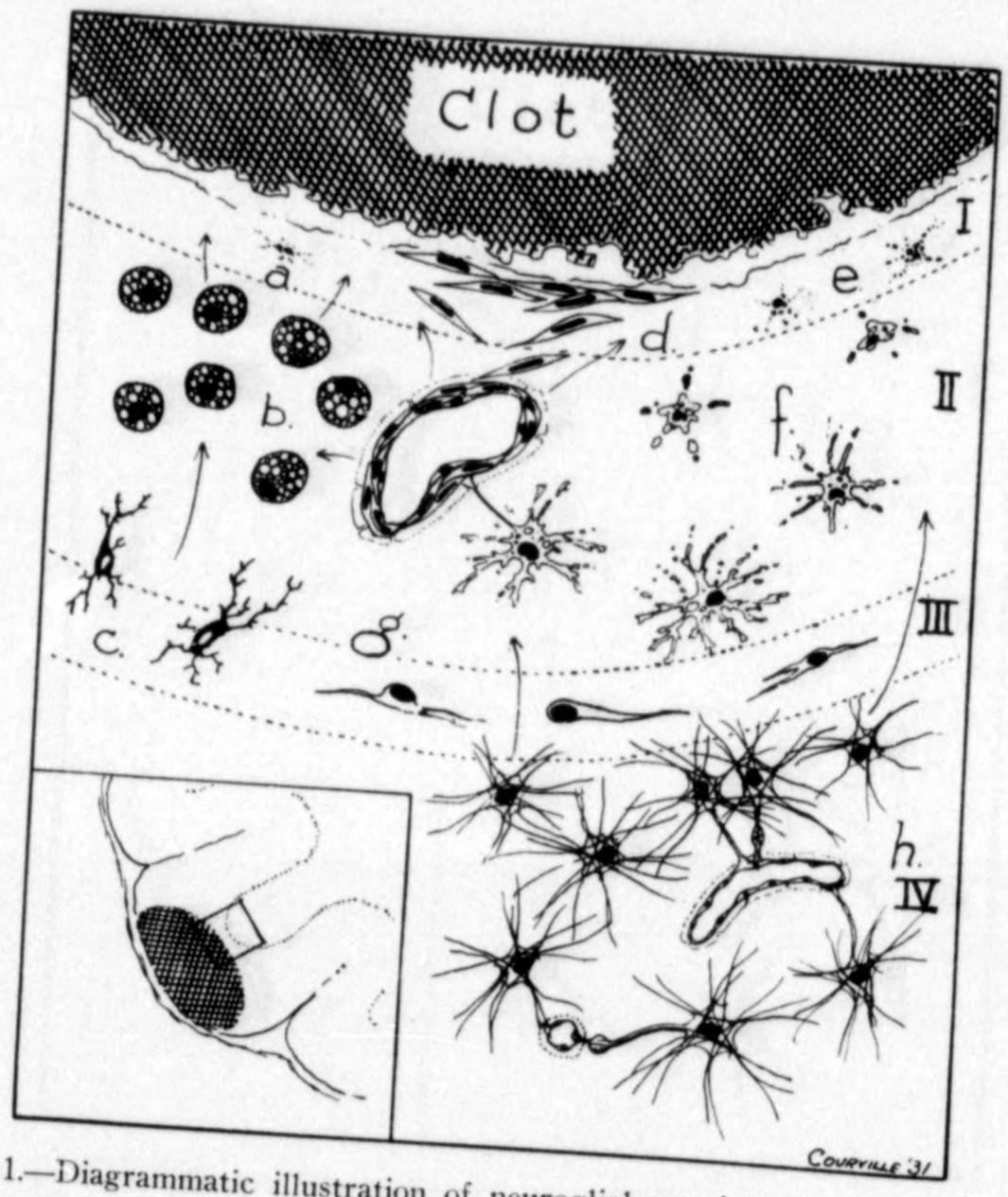

Fig. 1.—Diagrammatic illustration of neuroglial reaction to cortical contusion with hemorrhage (recent stage). The arrows indicate the direction of migration of various cellular elements. The insert shows the area included in the diagram (cortex of temporal convolution). *I* indicates the zone of immediate destruction; *II*, the zone of secondary or delayed disintegration; *III*, the zone of reversible reaction; *IV*, the zone of reactive gliosis; *a*, degenerating mesoglia within the zone of immediate destruction; *b*, compound granular corpuscles in the zone of late regressive change arising from the local mesoglia (*c*), or mesodermal elements of the blood vessel walls; *d*, proliferation of fibroblasts to form a narrow and incomplete zone of connective tissue; *e*, actively degenerating astrocytes; *f*, regressive changes in more distant astrocytes (ameboid glia); *g*, apolar, bipolar, unipolar and multipolar forms of astrocytes undergoing reversible reaction, and *h*, active proliferation of hypertrophied fibrous astrocytes.

stage of the process whether or not it is capable of surviving the injury. As will be subsequently shown, it is possible for a cell to lose many or even all of its processes and still retain its viability. It seems evident therefore that glia cells within this zone can and do regain in time their function and their normal morphologic aspects.

The distal zone, or *zone of reaction,* is characterized by hypertrophy and proliferation of the neuroglia. This region evidently is influenced by the injury only in so much as it serves as a stimulant to cellular activity, and here again the intensity of the reaction is apparently directly proportional to the distance from the injured area. Such zones are to be found most typically in the brain subjacent to the injury. The involved cortex, which is broken up by the contusion and subsequent hemorrhage, undergoes destruction more or less en masse. Destructive changes in such areas are more or less generalized and proceed with the same degree of rapidity. This is due no doubt to the profound disturbance in the cortical blood supply as well as to the original trauma. In one of our cases, however (case 20, with a survival period of five days), in which an extensively bruised area was marked by numerous fairly small hemorrhages, these various zones could be traced microscopically throughout the region. Midway between the various hemorrhagic spots were found comparatively normal astrocytes, while shading off on either side the typical stages of regressive change could be seen:

The essential changes in the development of these zones may be described as follows. There is a gradual widening of the original narrow zone of complete destruction as regressive changes come to involve the adjacent tissues. The astrocytes immediately adjacent to the injury soon lose their processes, and the cell bodies disintegrate. Their disappearance is followed by similar changes in the more peripheral cells for a variable distance, depending on the severity of the injury. This change does not proceed evenly throughout the tissue, for it is not uncommon to find cells undergoing complete destruction in regions where the neighboring astrocytes show little or no alteration. This may be explained either on the basis of a variation in individual susceptibility or on that of an irregular and uneven effect of the injury, possibly through interference with the blood supply. By the end of the first week, and probably within five days, this regressive change has become more or less stabilized, and does not spread to any great extent beyond the limits reached at this time.

The neuroglial reaction which ultimately results in the formation of a glial scar is the response of the uninjured peripheral astrocytes, together with that of more centrally situated cells, which have undergone a reversible reaction to resume their more or less normal activity. This reaction on the part of the neuroglia, as far as we are able to

determine, is a purely local and not a general phenomenon. It was difficult to find unquestioned evidence that direct cell division was taking place more than a few millimeters from the actual zone of injury. This has led us to believe that the neuroglial reaction from the standpoint of injury is a response to tissue destruction, and that as the destruction is local the reaction is local. The neuroglial proliferation is probably excited chemically by the products of disintegration which permeate the adjacent tissue for a limited distance. This would seem to controvert the conception that the remote sequelae of brain injury are due to diffuse general gliosis, a theory which has been held by some clinicians for many years.

Laceration of the Brain.—The conception of lacerations of the brain varies in the minds of clinical and pathologic observers. Every case of severe bruising is undoubtedly accompanied by direct or indirect tearing of tissue, as can be seen in histologic sections. We have considered, however, such minor manifestations to be a part of a contusion, and have reserved the term laceration to describe cases in which gross tearing of the brain has occurred. The latter is typically seen in persons sustaining comminuted depressed skull fractures with damage to the underlying brain. In these cases the greater extent of neuroglial reaction is directly dependent on the greater degree of injury. It is more difficult to make out distinct zones of reaction such as have been mentioned in local bruising. The essential features, as suggested in a person who survived a severe laceration of the brain for thirty-eight days (case 7), may be described as follows: The zone of destruction was much wider and more irregular, and came to be occupied ultimately by a fine reticulum in which nuclei were embedded (fig. 2). Scattered through this reticulum was found a black granular débris, much of which had been engulfed within phagocytes. The nature of these nuclei was difficult to determine, because no cytoplasm was demonstrated about them by the combined method of Penfield or by the gold sublimate, silver carbonate, reduced silver or Perdrau methods. In this zone were found patches of reacting glia and groups of macrophages evidently phagocytosing residual areas of débris. The bordering peripheral zone showed peculiar reactive forms of neuroglia of two essential types. The most conspicuous of the two were large, often multinucleated glia cells which had undergone hyaline change. The second, to be given more attention in later paragraphs, consisted of peculiar apolar, unipolar, bipolar or occasionally multipolar cells, which at first glance resembled the embryonic forms observed in the malignant varieties of the gliomas. Still more peripherally was found an irregular zone of gliosis in which the individual astrocytes had also undergone some degree of hyaline change (figs. 3 and 4).

The course of the changes following laceration may be briefly considered in this connection. The profound injury results in extensive masses of degenerating tissue, which are gradually removed by the macrophages. It likewise seems to result in a delayed and atypical neuroglial response, in which some unknown factor, perhaps an interference in blood supply, results in hyalinization of the reacting glia. The end-result, so well known by those who have had occasion to study

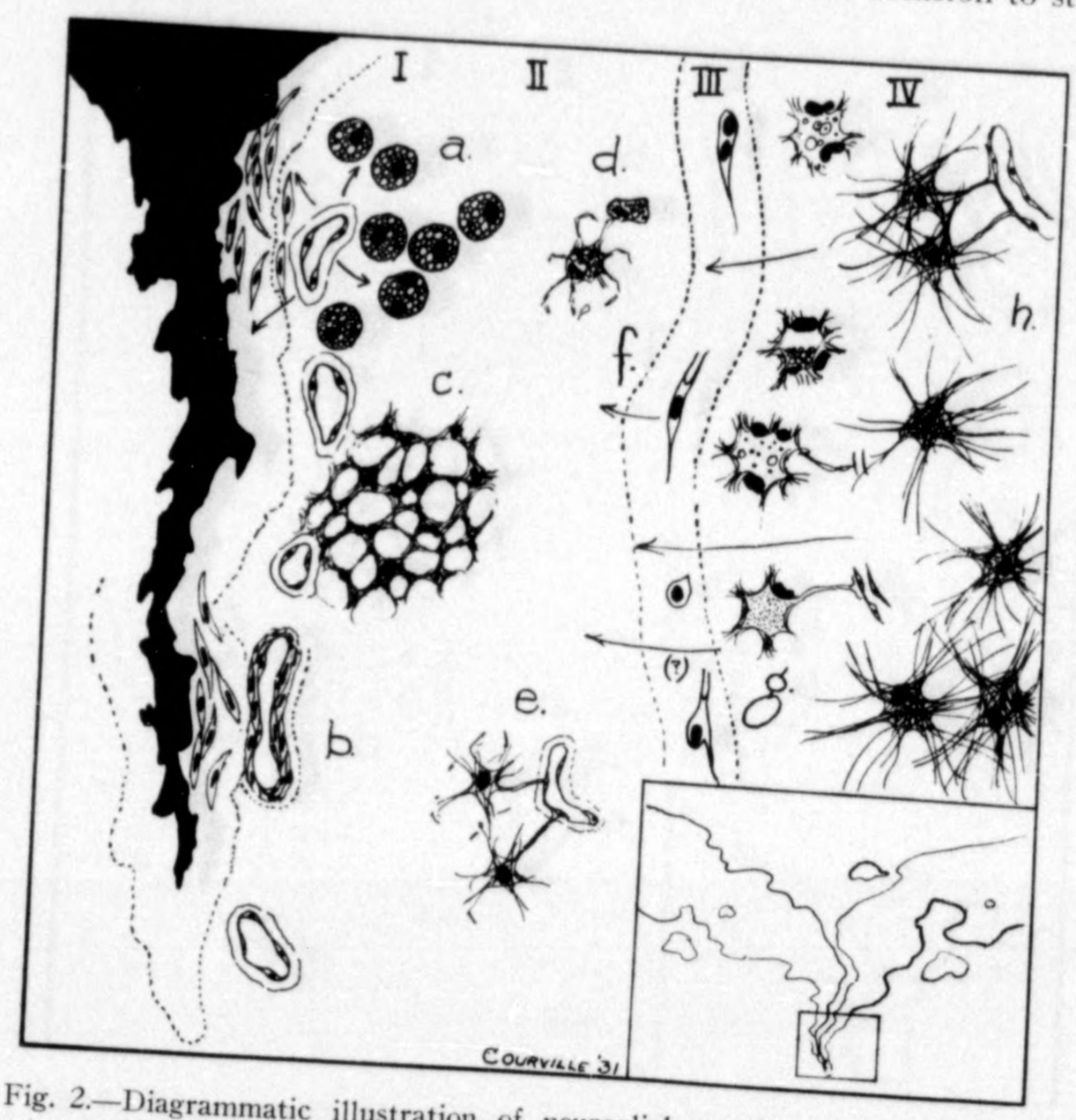

Fig. 2.—Diagrammatic illustration of neuroglial reaction to laceration (late stage). Actively degenerating astrocytes have been phagocytosed and removed. The arrows indicate direction of cellular migration. *I* shows the zone of immediate destruction; *II*, the zone of secondary or delayed disintegration; *III*, the zone of reversible reaction; *IV*, the zone of reactive gliosis; *a*, compound granular corpuscles arising from the mesodermal elements of the regional blood vessels (in white substance); *b*, proliferation of fibroblasts to form bordering connective tissue scar; *c*, filigree meshwork with hyperchromatic nuclei (? of neuroglial nature); *d*, dendrophagocytosis of slowly disintegrating astrocyte; *e*, patches of chronically altered neuroglia; *f*, apolar, bipolar, unipolar and multipolar forms undergoing reversible reactions; *g*, hyalinized multinuclear astrocytes (giant cells) showing regressive changes, and *h*, hypertrophy and proliferation of fibrous astrocytes.

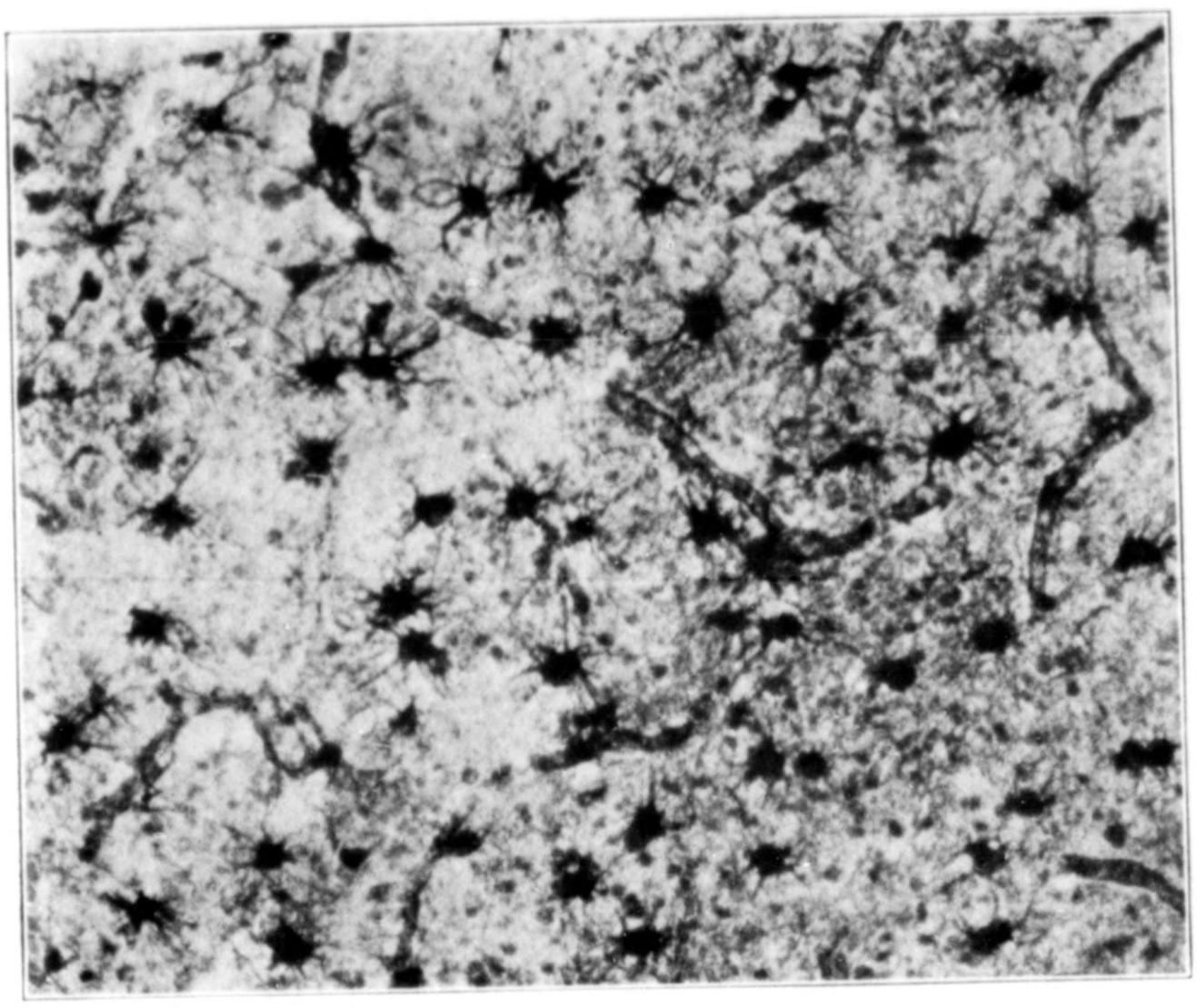

Fig. 3 (case 7).—Reactive gliosis adjacent to a thirty-eight day old laceration. Hypertrophy and direct cell division of astrocytes are shown. Gold sublimate method, × 220.

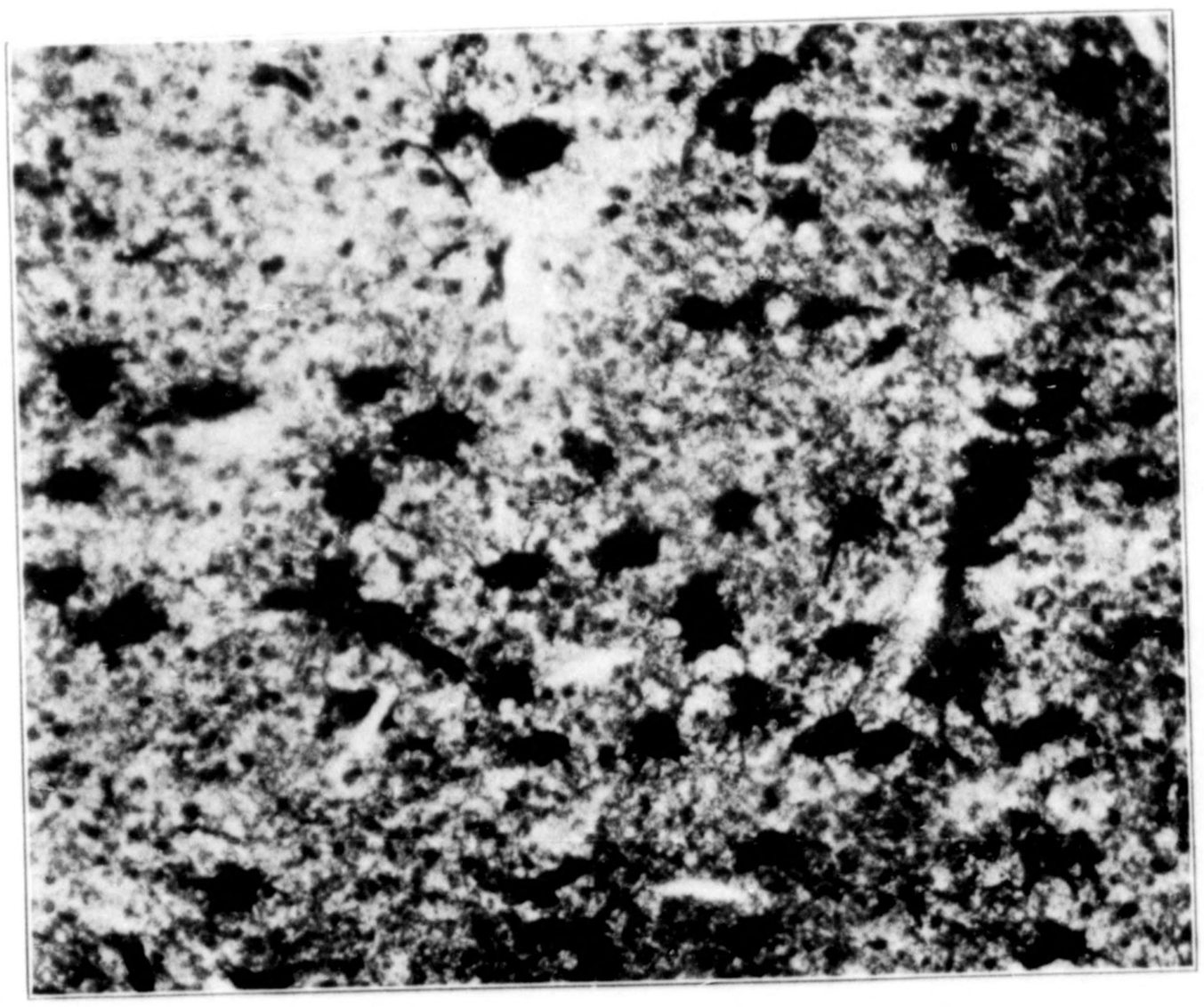

Fig. 4 (case 7).—Hyalinization of reacting astrocytes. The cell body is swollen, and expansions appear somewhat short and frayed out. Gold sublimate method, × 220.

the late effects of brain laceration, consists of a central connective tissue scar and an intense regional gliosis. We have had occasion to study such a case, not included in this series, illustrating this fact. In a child, aged 3, who had sustained a laceration of the right parietal cortex incident to forceps delivery at birth, a linear scar answering this histologic description was found. From this typical end-picture one must conclude that the loose reticular tissue becomes ultimately replaced by connective tissue, and that the atypical and incomplete gliosis is converted into a dense glial cicatrix. The fate of the hyalinized astrocytes and the "embryonic forms" remains an open question.

Neuroglial Reaction to Hemorrhage.—Hemorrhage is a common and often serious result of severe head injuries. The presence of blood in the cerebrospinal fluid is the rule. It would seem that the part played by free blood in the brain tissue from the standpoint of immediate or ultimate change has been given too little attention. Hemorrhages following injury may be classified as follows: (*a*) gross hemorrhages, either in the form of (1) extensive cortical hemorrhages following severe contusion, or (2) true traumatic intracerebral hemorrhages; (*b*) petechial hemorrhages (1) associated with cortical bruising or (2) regional petechial hemorrhages. The latter are incident to local dislocation effects as observed in the corpus callosum or due to severe local injury as occurs in the white matter of a lobe which has undergone extensive cortical bruising. There are, finally, (3) widely scattered petechial hemorrhages either due to sudden changes in the cerebrospinal fluid pressure or resulting from multiple fat emboli.

A few general considerations need to be emphasized before the details of neuroglial changes are described. A local clot or hemorrhage of any size immediately becomes a foreign body as far as the reaction of the surrounding brain tissue is concerned. Furthermore this "foreign body," through the degeneration of the red blood cells, disappears more rapidly than repair can take place, or multiple smaller hemorrhages may so break up fairly extensive portions of the cortex that degeneration en masse takes place.

Gross Cortical Hemorrhage: In any case of severe contusion a clot forms beneath the pia mater which is sometimes of considerable size. In this series we have not been able to trace the neuroglial reaction to its end-stage. Certain early changes have been observed. Judging from what takes place in gross cerebral hemorrhage and from the observations in old injuries of the brain, the lacking details may be supplied.

Any hemorrhage of consequence results not only in the destruction of the brain tissue in the space which it comes to occupy, but also in a zone of softening of the brain tissue at its margin. The glia cells in this zone undergo regressive changes during the first few days after injury, with the formation of ameboid glia cells as an intermediate stage

(fig. 5). The glia cells outside this zone undergo active proliferation, resulting in a zone of gliosis. Rapid degeneration of the red blood cells with subsequent phagocytosis results in the formation of a subpial or subarachnoid cyst, lined by a very narrow zone of connective tissue surrounded by a layer of neuroglia.

Traumatic Cerebral Hemorrhage: The reaction of neuroglia to traumatic cerebral hemorrhage is not unlike that due to other causes, as has been described by Globus.[27] He described three zones about cerebral hemorrhages. In early stages there was a zone of softening,

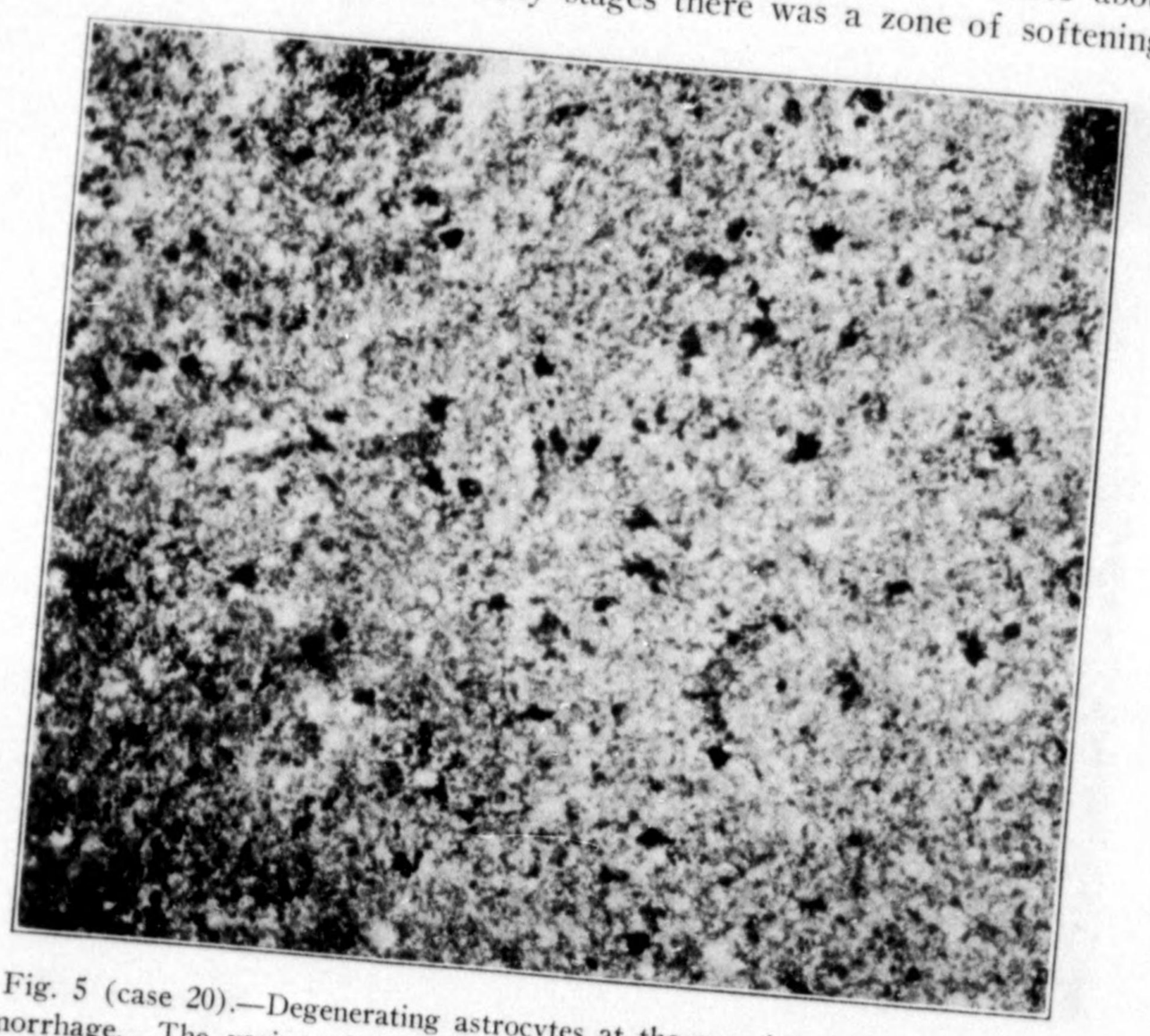

Fig. 5 (case 20).—Degenerating astrocytes at the margin of the small cortical hemorrhage. The various forms of acute degeneration are readily seen. Gold sublimate method, × 100.

a zone of vascular reaction, and finally surrounding this a zone of gliosis. In a later stage there was found an internal homogeneous structureless layer lining the cavity, a middle zone of phagocytes, astrocytes and a network of blood vessels. External to this was a third layer of intense gliosis. In this series we have three examples of gross intracerebral hemorrhage, one of thirty-one hours' duration

27. Globus, Joseph H.: Glia Response in Chronic Vascular Disease of the Brain, Arch. Neurol. & Psychiat. **20**:14 (July) 1928.