tures were diagnosed before a week of incubation; in only two instances did any of the flasks contain any growth and these were obviously contaminations. The cultures were made as a control of our work on transmission, but the results are independently important in that they show the difficulty in the cultivation of the typhus bacteria. To my mind they cast some doubt on the results of those experimenters who have reported the cultivation of bacteria on these ordinary media.

Our observation of bipolar organisms in the blood was later confirmed by Gavino and Girard,[22] by Nicolle[1] and by Hegler and von Prowazek.[10] I[23] have since reexamined the blood preparations made during our earlier study and feel quite certain that our findings are as significant as we then thought them to be. In reply to the criticism of Nicolle and others that these organisms are present in the blood in too small numbers to be accepted as the cause of the disease, I would call attention to the scarcity of bacilli in the blood of typhoid patients (*Typhus abdominalis*) and the difficulty in finding diplococci in the blood of pneumonics.

Following the publication of our observations appeared researches by Wilson[24] who cultivated a diplococcus in fifteen of thirty-three cases, and the investigations of McCambell[17] who observed organisms in the blood which gave the impression of being diplococci, but on closer study were shown to be bacilli with polar staining. McCambell made cultures on a variety of media, but all were negative.

In 1910 also appeared the publications of Predjetschensky[18] who observed in blood, urine and sputum an organism, usually rod-like, at times a diplobacillus, Gram-negative, non-motile, polar-staining. Cultures were positive in 100 cases when made between the sixth and ninth day of the disease, 2 to 5 c.c. of blood being implanted in 200 c.c. of broth, growth visible after twenty-four or forty-eight hours. The organism proved pathogenic for mice and guinea-pigs, was agglutinated by typhus serum but only in strong dilutions, 1:10 in one hour and 1:40 in four hours. Other immunologic tests are not reported, nor is there any proof that the animals for which the germs proved toxic had developed actual typhus fever.

Silberberg[25] in 1912 found in the cerebrospinal fluid a micrococcus which showed a clear middle zone, and Fürth[19] in 1912 described in the blood a short, thick bacillus with a clear central zone which proved cultivable in 38 per cent. of cases. The growth was difficult and polymorphous tendencies were exhibited on artificial media. Agglutination with typhus serum was indefinite and only a slight pathogenicity was found for apes, guinea-pigs and rats.

In 1913 Müller obtained cultures of a diplobacillus in five of eleven cases of typhus. The organism was Gram-positive at first, subcultures Gram-negative, slightly toxic for mice but non-toxic for macacus monkeys. He believes it the same organism as that described by Fürth, Rabinowitsch and Predjetschensky.

Finally and to my mind most encouraging, is the recent report of Plotz.[20] Plotz made anaerobic cultures of typhus blood, which in my opinion was a wise procedure, and, although his methods are not described in the preliminary report, he seems to have succeeded in obtaining eleven positive cultures in twelve cases of typhus fever, six of these being the milder Brill's disease. The cultures when injected into guinea-pigs produced a febrile reaction similar to that which occurs after inoculation of typhus blood. Complement deviation was obtained in six of eight cases, using an antigen made from the bacillus and serum from patients after crisis. The morphologic description is as follows:

> The organism is a small Gram-positive pleomorphic bacillus from 0.9 to 1.93 microns in length, the breadth being from one-fifth to three-fifths the length. It is non acid-fast, has no capsule or polar bodies and can be demonstrated with appropriate methods.

This description agrees rather closely with that of the structures observed in typhus blood by Ricketts and myself and with the observations of several of the more recent investigators. It would seem that many of us have been interested in the same organism. If later work bears out these earlier studies, typhus fever must be included in the group of insect-borne bacterial diseases and grouped together with plague and Rocky Mountain spotted fever. It is worthy of note that both of these diseases are caused by bipolar bacilli that resemble the organism probably responsible for typhus. This close relationship of typhus with plague and Rocky Mountain spotted fever was suspected by Ricketts some time before our investigations of typhus were undertaken.

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22. Gavino and Girard: Nota preliminar sobre el Tifo experimental en los Monos inferiores, etc., Publ. del Institut Bacter. Nacional de Mexico, 1910.
23. Wilder: The Problems of Transmission in Typhus Fever, Jour. Infect. Dis., 1911, ix, 11.
24. Wilson: The Etiology of Typhus Fever, Jour. Hyg., 1910, x, 155.
25. Silberberg: Bakteriologische Untersuchung der Zerebrospinalfluessigkeit bei Typhus exanthematicus, Ref. Centralbl. f. Bakteriol., 1912, liii, 327.

STUDIES CONCERNING DIABETES*

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The work, of which this paper will give a synopsis, is the continuation of an experimental study of diabetes described in detail elsewhere.[1] Certain of the results of the previous investigation, bearing on the present topic, may be summarized under the following four headings:

1. Production of Diabetes: Removal of portions of the dog's pancreas produces a lowering of the sugar tolerance. Removal of nine-tenths of the gland results in severe diabetes. When the remnant is larger (for instance, one-eighth), milder types of diabetes result. The course is chronic, extending over months, and the end fatal. Such animals furnish a closer imitation of human diabetes than is produced by total pancreatectomy.

2. Pathologic Anatomy of Diabetes: In the foregoing procedure, duct communication between the pancreatic remnant and the duodenum is preserved. Therefore the acinar tissue does not atrophy, and in some cases it may hypertrophy. The islands of Langerhans show typical progressive alterations, which may be summarized as vacuolation of cytoplasm and loss of granulation, pyknosis of nuclei, loss of cells, and

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* From the Hospital of The Rockefeller Institute for Medical Research.
1. Allen, Frederick M.: Studies Concerning Glycosuria and Diabetes, Harvard University Press, Cambridge, Mass., 1913.

finally disappearance of islands. By suitable controls the changes were shown to be specific to diabetes. Homans[2] has made a careful histologic study of such changes in the islands of diabetic cats by the aid of the admirable methods of Bensley.

3. Pathologic Physiology of Diabetes: An idea has long existed that the disturbance of carbohydrate metabolism in diabetes might perhaps be explained by the assumption that sugar exists in a combined form in the normal body, but that this combination is lacking in diabetes. In the diuretic behavior of dextrose in diabetic and non-diabetic animals, I found contrasts which were interpreted as evidence in favor of this conception, which was therefore put forward as a hypothesis to explain the various phenomena of diabetes. The combining substance was designated by the figurative title of "amboceptor," to indicate its function as a bond between tissue and sugar. The substance which thus combines with dextrose, or some link in the combination, is supposed to be furnished by the islands of Langerhans. For details concerning the hypothesis and the evidence, reference must be made to the original publication.

4. Prevention or Checking of Diabetes: Under certain conditions the presence or absence of experimental diabetes may be determined by the patency of the pancreatic duct. When the pancreatic remnant is sufficiently small, diabetes results, even if this remnant is cut off from duct communication. But, with a slightly greater size of pancreas-remnant, it is possible under favorable conditions in certain cases to show that diabetes occurs if the duct is patent, but remains absent if the duct is ligated. Particularly in one instance it was shown that a diabetes already begun stopped when the duct was ligated. The period during which diabetes can thus be prevented is necessarily limited, since ligation of the duct produces in the dog gradual atrophy and degeneration of all the elements of the pancreas, and this gives rise after weeks or months to the Sandmeyer type of diabetes.

PRESENT INVESTIGATION

The present research has advanced along the same lines as the preceding one, and has kept in view the same clinical purpose.

I. PRODUCTION OF EXPERIMENTAL DIABETES

A. By Operation

Of several species of animals tried, the dog and cat are the most convenient and useful. Rapid death from cachexia, which I previously described as an occasional occurrence in dogs, is more frequent in cats. In them diabetes is intense and life short after removal of nine-tenths of the pancreas; but by removal of fractions such as three-fourths, four-fifths and five-sixths of the pancreas, one obtains mild or severe forms of diabetes as desired, and such cats live for weeks or months. In cats, more readily than in dogs, can thus be produced mild, transitory, intermittent forms of glycosuria, doing the animal little or no harm, and determined largely by diet (as milk, or sometimes even the feeding of liver instead of ordinary meat). There is a decided tendency toward recovery, though aggravation can often be produced by continuance of improper diet. This form of diabetes may be compared to those mild, intermittent, relatively benign human cases which some persons have supposed to be not of pancreatic origin.

With respect to dogs, the figures given above concerning size of pancreas-remnants hold good for medium-sized animals, such as were convenient for the purposes of the previous research. Present findings indicate that the size of the pancreas in proportion to body-weight in large and small dogs may vary considerably, and that the size of the pancreas-remnant which permits diabetes may vary correspondingly, though a longer series of observations must be completed before making more precise statements. In cats variations of this character are absent or less marked.

B. By Diet

The papers of Thiroloix and Jacob, previously reviewed, report success in a line of experiment in which earlier workers failed. They state that some dogs after partial pancreatectomy are free from glycosuria on meat diet, but show glycosuria when carbohydrate is fed; and that continuance of carbohydrate diet finally brings the animals into a state of severe diabetes in which they excrete sugar even on meat diet. The reports of the French authors are brief, and contain no mention of controls or proof that such dogs might not ultimately develop severe diabetes, even without carbohydrate feeding. These may perhaps be the reasons why this discovery has received practically no notice in the literature. Independently of these writers I had made similar observations, and believing them to be of importance, I have repeated and extended the work. Based on the experiments so far conducted, it is possible to make the following statements:

1. After removal of sufficiently large fractions of the pancreas, as above described, dogs develop a severe diabetes, in which they show heavy glycosuria on meat diet and also during considerable periods of fasting. The condition progresses steadily downward to a fatal end.

2. When the remnant of pancreas left *in situ* is slightly larger, a condition may be produced in which the fate depends on the diet. On meat feeding such a dog is free from glycosuria and remains so for months, eating his fill every day and maintaining full health and nutrition, with no sign of downward progress; but subcutaneous tests show that the dextrose tolerance is very low, and bread feeding readily produces glycosuria. A return to meat diet stops the glycosuria; but if the bread diet and accompanying glycosuria are maintained for too long a time, the glycosuria then continues, even on meat feeding. The diabetes thus produced is not inferior in severity to that resulting from simple removal of larger fractions of pancreatic tissue, and the downward course and fatal termination are similar.

3. When the pancreas-remnant is still larger, glycosuria is absent on meat diet, and on bread diet may be absent or transitory. Such animals may remain in excellent condition indefinitely on bread diet, free from glycosuria or any downward tendency; but if sufficient sugar is added to the diet, glycosuria can be produced and maintained. After a period of such glycosuria, the animal reaches a condition in which it is glycosuric on bread diet. By prolonging the glycosuria on bread diet, the dog finally reaches the condition of severe diabetes, with glycosuria on meat diet, and continuous downward progress. For such sugar feeding I have ordinarily used commercial glucose. The

2. Homans, John: Jour. Med. Research, 1914, xxx, 49.

experiments succeed best in greedy dogs and those naturally fond of sugar. A decided aversion to sugar on the part of the dog may spoil such an attempt through failure of appetite.

4. When the pancreas-remnant is still larger, sugar feeding may produce transitory glycosuria, but it cannot be made to continue. The sugar tolerance is lower than in normal dogs, but nevertheless the doses of sugar necessary to produce glycosuria are higher than can be tolerated as a daily routine by the gastro-intestinal canal. Persistence in the attempt to maintain glycosuria causes diarrhea and illness. The dog refuses to eat, sugar given by stomach-tube is vomited, and true diabetes remains absent. Similar results can be obtained with cats by feeding carbohydrate in the form of milk.

The changes previously described as occurring in the islands of Langerhans occur whether the diabetes follows directly on the operation alone, or has been induced in the prepared animal by means of modification of diet. The best of the control animals are still alive; but the control tissues thus far examined indicate that in animals predisposed by operation, when diabetes is prevented by carbohydrate-free diet, the signs of exhaustion and degeneration in the islands of Langerhans are absent. If further study shows that this is the case, it will afford additional evidence that these changes have a direct relation to the diabetes and that they are a result of functional overstrain.

While various factors are undoubtedly concerned in the production of human diabetes, clinical observations indicate that diet is an important one. It is generally recognized that there is a higher incidence of diabetes among those races or classes of people who use an excess of carbohydrate. Luxurious living and sedentary life are thought to predispose to this disorder. The experimental observations on animals suggest an explanation of this relationship between diet and diabetes in the human subject. If individuals differ in the strength of the pancreatic function as in other functions, in some this may be so weak that diabetes comes on in early life irrespective of the diet. In others this function may be only a little stronger, so that diabetes may be delayed until later in life or even to the period of senility, when there occurs an impairment of various functions. Others may be more or less below the average in pancreatic functional power, but under ordinary circumstances this is sufficient to prevent the occurrence of diabetes. In these persons, however, who might otherwise go through life with no sign of diabetes, an excess of starch in the diet may serve as an exciting cause of diabetes, and the degree of such excess may help to determine the earlier or later onset and the milder or severer type of the disorder. In other persons of this sort, as in the corresponding type of dogs, the pancreatic function is able to deal safely with as much starch as can be digested, but a sufficient excess of sugar is an effectual cause of diabetes.

It is impossible to produce diabetes in the normal dog by an excess of carbohydrate feeding, since if too much sweet or starchy food is taken, indigestion results and automatically stops the ingestion. But in dogs after operation and in predisposed human patients, pancreatic weakness may reverse the normal relation, so that the organism can digest and absorb more carbohydrate than it can combine and assimilate; and in this condition the production of diabetes by improper diet is possible. The question of diabetes may then be regarded as a balance between the digestive and assimilative functions. Moreover, the body is equipped with no natural safeguards against this unnatural condition. There is no reflex or other mechanism which points plainly to the cause of the trouble and compels its cessation. On the contrary, the impaired nutrition due to failure of assimilation affects the organism as if it were due to deprivation of food. The response commonly shows itself in the harmful form of increased appetite. The taking of excessive food injures the assimilation still further, and thus a vicious circle results.

II. PREVENTION OR CHECKING OF EXPERIMENTAL DIABETES

The therapeutic experiments in animals pertain to two groups of cases, those in which diabetes is produced by simple operation, and those in which diabetes is produced by diet in predisposed animals.

1. Animals made diabetic by operation. In animals from which an excessive amount of pancreatic tissue is removed, a diabetes may be obtained which is so severe that fasting will not produce sugar-freedom. But when the pancreas remnant is of suitable size, for example, one-tenth, though the resulting diabetes is permanent on meat diet and will end fatally if allowed to persist, nevertheless a few days of fasting at the outset will produce sugar-freedom. If the diabetes is allowed to continue longer, a much longer period of fasting may be necessary for sugar-freedom, or it may be impossible to obtain. If, after obtaining sugar-freedom, feeding of protein and fat (with occasional bones) is begun very cautiously, in quantity only enough to maintain the animal in its thin condition, such dogs remain free from diabetes. The longest experiment to date is that of a dog which, possessing less than one-tenth of the pancreas, has been kept free from diabetes for six months, and there is at present no indication that the condition cannot be continued indefinitely. If an attempt is made to increase the weight of such an animal, glycosuria soon appears and must be checked by renewed fasting. Such dogs, though very thin, are vigorous and lively. They contrast sharply with dogs which, after similar operations, are allowed to remain diabetic on full meat diet. Though the latter animals at first appear much better nourished, they finally emaciate in spite of the most enormous eating; and when they have become as thin as the dogs above described, weakness and cachexia are very evident, and the progress continues downward to death.

2. Animals made diabetic by diet. When the animal possesses perhaps an eighth or a sixth of the pancreas, and is not diabetic after operation but is then made diabetic by excess of carbohydrate, this diabetes at first can be stopped by a simple change to meat diet. After a longer duration, the diabetes no longer stops on carbohydrate-free diet; but after a period of fasting, the time depending on the severity of the diabetes, the urine becomes sugar-free. With still greater duration or severity of the diabetes, sugar-freedom is no longer obtainable by fasting. When such animals are made sugar-free, they may be kept so by the same procedure as described for those of the former group. When the diabetes is thus checked fairly early, it is evident that the prognosis is much more favorable than in animals of the previous group, for in the present animals the removal of pancreatic tissue was considerably less, and the cause of the diabetes is partly a functional change. Accordingly, it is found that the

diet can be gradually increased, and in favorable cases the animals be brought to a higher level of weight and nutrition than is ever possible with dogs of the preceding type. Up to the present, however, the experience has been that these dogs are never able to return quite to the condition which they enjoyed before the diabetes, and which is permanently maintained by similar dogs in which diabetes is prevented by suitably chosen diet from the outset. As above mentioned, dogs so treated can be kept indefinitely at full weight and well-being when placed after operation on a diet which keeps them free from glycosuria. But when diabetes gravis has been produced and allowed to continue long enough to demonstrate its reality, while it has been possible by the foregoing method to stop the diabetes and bring a dog back to within a kilogram of its normal weight, every attempt to produce a further gain in weight has brought a return of glycosuria, which must be checked by fasting. Such dogs, however, are so near to normal that, if they are mixed up in a yard with ordinary dogs, a stranger might be unable to tell one from the other.

The microscopic examinations of the pancreas remnants of such animals as have yet come to necropsy from both of these groups show that in both alike the island cells are well endowed with cytoplasm and granules, and degenerative processes are not seen; but there is a decided impression that the islands are inferior in both size and number to those of normal animals. If this impression proves valid in further experiments, a correlation readily suggests itself between the observed anatomic change and the diminished pancreatic function described in the preceding paragraph.

In my previous report I have shown that by removal of suitable fractions of the pancreas, animals may be brought so close to the verge of diabetes that the removal of less than a gram of additional pancreatic tissue suffices to bring on diabetes. According to the "amboceptor" hypothesis, the pancreas furnishes some definite substance or substances used by the cells of the body for the metabolism of carbohydrates and perhaps also of other foods, the "amboceptor" being used up in metabolism and bearing some quantitative relationship to the metabolism. Extending this theory to the foregoing experiment, one may say that the fragment of pancreas which barely prevents diabetes is the smallest fragment which can supply the minimum quantity of "amboceptor" necessary for the animal's metabolism. When such a pancreatic fragment is even slightly reduced, the supply becomes slightly deficient in quantity, and diabetes accordingly begins and runs the usual downward course.

Present observations prove that the reverse of this experiment is likewise possible, that is, when an animal and its food consumption are suitably reduced, a pancreatic remnant otherwise inadequate becomes adequate; diabetes under these conditions may be prevented or be checked after it has appeared. Prevention or cessation of diabetes previously observed in consequence of ligature of the pancreatic duct may be explained by the impaired food absorption and chronic malnutrition of the animal. Similarly in dogs which develop distemper after the pancreatic operation, and which therefore refuse food and emaciate rapidly, diabetes may fail to appear or may stop after it has appeared. Interpreting these experiments on the basis of the "amboceptor" hypothesis, one may say that an otherwise insufficient amount of "amboceptor" may become sufficient when the metabolism of the body is artificially diminished.

III. CLINICAL TREATMENT OF DIABETES

In the clinical literature of diabetes there are authentic reports of certain cases in which even severe diabetes has cleared up spontaneously and completely on the onset of cirrhosis of the liver, cancer, tuberculosis or some other wasting condition. Other cases have notably improved. Probably the most severe and certainly the best studied of such examples was presented by one of Joslin's patients,[3] in whom a long-standing and dangerous acidosis disappeared entirely, and a negative carbohydrate balance became positive, following the onset of tuberculosis. When these cases are considered in the light of the experimental study of animals, the possibility is suggested that we have an indication for a rational method of dealing with diabetes, or impaired pancreatic function associated with overstrain.

Notice should be taken of the advantage possessed by most diabetic human patients over diabetic dogs. Even the most hopeful of the above-described dogs has only a small fraction of the pancreas. Most of the organ is hopelessly gone, and the presence or absence of diabetes is determined by functional influences acting on the little remnant. Furthermore, even when the diabetes is inaugurated by functional means, the organic degenerative changes quickly ensue in the islands of Langerhans. Under these conditions it is surprising that results are obtainable by treatment at all. On the contrary, in typical human diabetes the entire pancreas is present, and there are indications that functional disturbance is an important factor.

It has been thought justifiable, therefore, to undertake the treatment of a limited number of patients by a method based on the principles derived from the experimental work as indicated in this communication. The number of patients so far treated is limited, but the results obtained indicate that the same method employed in rendering the diabetic dog free of glycosuria and prolonging its life is efficacious in eliminating glycosuria and acidosis in the human patient. To what extent life may be prolonged by this method only a large statistical study will show. The observations so far indicate that the method is not harmful, and when carried out carefully seems definitely beneficial.

The method of treatment is in brief as follows: If the patient is moderately emaciated, with a negative carbohydrate balance and acidosis, he is put to bed and receives no food whatever. If coma seems imminent the usual emergency treatment with purging, stimulants, alkalies and large amounts of water should, of course, be carried out. In addition to fasting, alcohol is important in the treatment at this stage. From 50 to 250 c.c. of whisky or brandy may be given in each twenty-four hours in small doses, from 10 to 20 c.c. every one to three hours during the twenty-four. As soon as the glycosuria stops and the acidosis diminishes, which even in severe cases may be within forty-eight to ninety-six hours, the amount of alcohol and alkali may be reduced. Fasting and moderate dosage of alcohol are continued for from twenty-four to forty-eight hours longer, however, depending on the patient's strength. The alkali is now stopped, and feeding with starch is commenced in order to clear

3. Benedict, Francis G. and Joslin, Elliott P.: A Study of Metabolism in Severe Diabetes, Carnegie Institution of Washington, 1912, Case R, p. 55.

up the last traces of ketonuria. The kind of starch is of minor importance. Green vegetables are useful because their carbohydrate and food value is so low that they can be given in considerable bulk, and this bulk is agreeable to the patient for relieving his feeling of emptiness. Neither fat nor protein is added. For the first day, the food is chosen to represent a carbohydrate content of from 10 to 40 gm. This is divided into four to ten equal portions and fed at equal intervals during the day. If glycosuria remains absent, the ration for the next day is doubled, to represent 20 to 80 gm. of carbohydrate, similarly divided into numerous small portions. On the next day it is sometimes possible to increase the ration to 100 gm. of carbohydrate, without glycosuria. About this time, especially if glycosuria has appeared, another fast-day is interposed, from 50 to 200 c.c. of whisky being given. Present experience indicates that even in severe cases ketonuria may by this method be made to disappear entirely. Several repetitions of the foregoing routine may be necessary for this purpose. All food contains danger, tending toward either glycosuria or ketonuria. The carbohydrate of the diet is seldom reduced below 50 gm., and is preferably kept higher. If carbohydrate must be kept low, the total diet is kept low. The diet is so chosen that glycosuria, not ketonuria, is the signal of overstrain. Fasting-alcohol days are given not merely whenever this signal appears, but also at close enough intervals to prevent it from appearing, even every two or three days if necessary. If there has been no glycosuria, a slight addition to the diet is made after each fast-day. Each day's diet is calculated exactly, and the nitrogen-balance is watched. It is thought that no matter how low the assimilative power, the attempt to feed in excess of this power is harmful, and it is possible that by rest the assimilative function may gradually become stronger. With improvement in the patient's condition, the carbohydrate in the diet is further increased. Increase in weight, however, is not attempted at this time. From our present point of view, contrary to the generally held opinions, the attempt to increase weight should be the last rather than the first step in treatment. It is attempted to keep the metabolism at the lowest safe level until the patient is taking from 100 to 150 gm. of carbohydrate (mostly as green vegetables) daily, with fast-days interposed often enough to prevent any trace of glycosuria from appearing. Then protein is cautiously added, always being kept rather low; and in favorable cases the weight and well-being may finally improve under gradual additions of fat.

The radical procedure here described is that used for the most severe cases. In milder cases the treatment may be correspondingly milder. Primary loss of weight is intentional. The purpose of the treatment is not to confer temporary comfort or appearance of well-being, though various symptoms, including polyphagia and asthenia, may actually be relieved. When there is extreme cachexia and emaciation, the difficulty is greatest. It may then be necessary to juggle very carefully the three factors of glycosuria, acidosis and nutrition.

A report giving the results of this form of treatment in a series of cases will be published later. It is felt that the conception underlying this method of treatment, based on experimental observations, is new, though certain details have long been recognized as of importance. According to this method, alkali treatment is not employed, unless for a brief period at the outset, while severe acidosis is being combated. The alkali treatment has been called the most brilliant discovery in the modern study of diabetic therapy. It is indeed a valuable means for facilitating the excretion of acetone bodies. But under an efficient treatment of diabetes, acetone bodies should not be excreted. They should be burned.

Though it seems possible thus to check all active symptoms, with apparent benefit, even in very severe cases, yet it is felt that the ultimate outlook for these patients is far less favorable than it would be if they could be treated earlier. The best therapeutic hope is believed to lie in the application of this principle of treatment at the earliest possible stage in diabetes.

ABSTRACT OF DISCUSSION

PROF. A. J. CARLSON, Chicago: Does Dr. Allen consider the evidence conclusive that mere obstruction of the pancreatic duct in dogs leads to the atrophy of all the elements in the pancreas? In the rabbit this is not the case. I have seen in dogs, in connection with other work, the islands persist for six or nine months, that is, enough of the island tissue to prevent diabetes.

DR. ALLAN C. EUSTIS, New Orleans: Has Dr. Allen noticed the appearance of the acetone bodies in the urine of these dogs; whether they were present during the fasting stages and how soon they would appear; and also whether the amount of the pancreas left in had anything to do with the rapidity with which the acetone bodies appeared?

DR. F. M. ALLEN, New York: Answering the latter question first, I have never seen a satisfactory reproduction of human acidosis in dogs. A few authors have reported considerable acidosis in totally depancreatized dogs, and even death in coma, but these cases are the exception rather than the rule. The difference between carnivorous animals and man as respects acidosis is one reason for attempting to reproduce diabetes in other species which are more like the human in this respect. With regard to Dr. Carlson's question, two factors must be considered; one is species, and the other is time. In rabbits and guinea-pigs, following ligature of the pancreatic duct, authors have proved that numerous normal-appearing islands of Langerhans are present long after the disappearance of all acinus tissue. The pancreas is described as being replaced by fibrofatty tissue and though the islands pass through phases of degeneration and regeneration, the island tissue is not permanently destroyed but apparently persists indefinitely. Such animals are free from diabetes, but it has never been proved that true diabetes can be produced in these species by any means. In dogs, on the other hand, ligature of the pancreatic duct is followed by scar-tissue formation, and islands as well as acini are destroyed. Such degeneration of a ligated pancreas-remnant gives rise to the Sandmeyer type of diabetes. In the dense fibrous tissue at the site of the pancreas in dogs dead from prolonged Sandmeyer diabetes, it is said that neither acini nor islands have been found. The time-element is involved in experiments such as Macallum's, which undertake to show that islands persist at a time when all acini have disappeared, and that the dog at this time is not diabetic. Positive results in such experiments may furnish evidence in favor of the insular hypothesis; nevertheless after a longer time-interval the islands may be expected to degenerate and disappear. Indefinite persistence of islands in the ligated pancreas, as proved for the rabbit, has never been shown in the dog.

The Eye Sees Only What it is Trained to See.—How many eyes—yes, and skilled eyes, too—looked at the thorax and never saw the so-called Litten's sign or diaphragm phenomenon? Many of us look at it every day and fail to see it, even after we know about it. How often does the diagnosis of a thoracic aneurysm go begging for want of a careful glance?—Thomas McCrae, *Canadian Med. Assn. Jour.*