1916

Frederick M. Allen, 1916

The Rockefeller University

THE ROLE OF FAT IN DIABETES*

FREDERICK M. ALLEN, M.D.,

Hospital of the Rockefeller Institute for Medical Research, New York

THE work with diabetes at the Hospital of the Rockefeller Institute began with feeding experiments on partially depancreatized dogs, and since then has grown in various directions. The results have been applied in the treatment of human cases, and this side of the investigation has been taken up by Drs. Stillman and Fitz, Dr. Stillman having studied especially the carbon dioxide changes in alveolar air and blood and Dr. Fitz the acetone bodies in blood and urine. It was a great good fortune when Dr. DuBois consented to determine the respiratory metabolism of certain patients at the Russell Sage Institute, and thus (in connection with the similar findings of Benedict and Joslin) some facts were established which were important for the intelligent application of the clinical treatment, and some theoretical questions decided and some others opened up. On the side of the animal experiments, Dr. Palmer has carried out a research in the practically unknown field of the sugar-content of the tissues under normal and various pathological conditions. Dr. Perlzweig and Miss Wishart are assisting in several problems, comprised chiefly under the topic to be discussed. The combination of animal and clinical work is very advantageous, each throwing light on the other. Also, the animal experiments are different from the customary, in that they do not consist in brief observations limited to a single point, but, on the contrary, animals are brought into the desired diabetic or other condition, and then are studied like human patients, through months and years if necessary. This plan has always appeared to me as indispensable for real progress in certain aspects of this problem. Acute experiments cannot give the best picture of chronic disease. Chronic

* Delivered November 4, 1916.

conditions in animals need to be studied by the same combination of clinical, chemical, and microscopic methods as used for human patients, and for the same reason, namely, that one part of the picture can be understood only in relation with the other parts. On this plan, information is gained by determining the means to produce in animals the conditions occurring spontaneously in patients, and then by studying these conditions with the freedom and accuracy which are possible in animal experiments.

The problems of diabetic and normal metabolism are being opened up with surprising rapidity as methods become available. The monograph concerning my research at Harvard was written in 1912, and at that time comparative analyses at frequent intervals as shown in these charts were impossible, because the methods then existing required too much time or material. The present work was done entirely with methods published by American chemists within these few years. The numerous blood-sugar analyses were made possible by the method of Lewis and Benedict, which was used unmodified as originally described. The analyses for acetone bodies were carried out first with a modification of the methods of Shaffer, Marriott, and Folin and Denis, and later by the recent Van Slyke method. The alkaline reserve of the plasma was estimated by Van Slyke's simple and accurate device of the carbon dioxide combining power, which has proved its usefulness both experimentally and clinically. The blood-fat was determined by Bloor's method in the modification employed by Murlin and Riche. The methods introduced by Sellards and by Levy, Rowntree and Marriott deserve mention in connection with the study of acidosis, but had to be omitted in this research. It is evident that various blood and urine examinations, calorimetric studies, tissue analyses, and histologic and other investigations are most instructive when performed not upon different animals but upon the very animals for which these other data exist.

It has been decided to discuss the rôle of fat in diabetes because of its theoretical and practical importance, and because it has constituted one of the most confused and perplexed phases of the subject, where any light from any source may be deemed

desirable. The feeding experiments mentioned at the outset have included the feeding of fat, and this has involved the longest and most difficult experiments of the series. Therefore, this opportunity is taken to present the results of some of the experiments in this direction, and this paper will consist largely of observations not heretofore published.

It was formerly impossible to make a satisfactory study of this question with animal experiments because only two types of diabetic animals were known, namely, the Minkowski type with total extirpation of the pancreas, and the Sandmeyer type with removal of most of the pancreas and isolation of the remainder from its duct communications, so that the blocking of secretion brought on sclerosis and atrophy. Neither of these types of animals is capable of digesting and absorbing enough fat for the purpose, or of affording in other respects a sufficiently close reproduction of human diabetes, where there is ordinarily no deficiency of pancreatic digestion. I have previously described a method which gives a good approximation of the clinical condition. Those familiar with the publication will recall that this consists in removing most of the pancreas, leaving a remnant ordinarily of one-eighth to one-twelfth always communicating with a duct. With the smaller remnants the diabetes is severe; with the larger remnants it is mild; but by feeding the animals beyond their tolerance, so as to maintain a prolonged glycosuria, there is progress downward, as in human cases, and the mild diabetes becomes as severe as that which follows the more extensive removal of pancreatic tissue. For our present purpose and for most purposes the best results are obtained by having the pancreas remnants as large as possible, for two reasons. One is the avoidance of cachexia. The totally depancreatized dog dies within a relatively brief period, while an equal loss of sugar and nitrogen caused by phloridzin is far better borne. Some dogs with very small pancreas remnants do fairly well, but a large proportion of them fail to thrive, gradually emaciate, and die; whereas dogs with larger remnants but equally severe diabetes thrive much better. Nothing is known concerning the nature of this peculiar pancreatic cachexia; presumably it repre-

sents metabolic failure. The second reason referred to consists in the power of digestion. The digestion of the partially depancreatized dogs is never quite equal to the normal. Some of the diets used tax the digestion of normal dogs. In particular, the larger the pancreas remnant the better do the dogs dispose of a high fat diet. Occasional dogs become diabetic with exceptionally large pancreas remnants, and such animals are valuable for this use. In general, the program is to choose young dogs as strong and as voracious as possible. The pancreatic tissue removed is the minimum required to produce mild diabetes. The tolerance is then broken down by overfeeding, the diet sometimes including several hundred grams of glucose daily until the desired degree of diabetes results. The animals are then often kept free from glycosuria for several weeks or months, and any tendency to recovery of too high a tolerance is checked by a period of overfeeding. In the best cases there is thus a decided hypertrophy of the acinar tissue, so that the remnant may come to equal as much as one-fourth of the original weight of the pancreas, and yet the diabetic condition is maintained. Such dogs have highly satisfactory vitality and digestive power, and are very well suited for the fat feeding and other experiments. Though the internal secretory function has thus been injured largely by functional means, it remains fairly constant at its low level, and any recovery of tolerance is exceedingly slow. In this respect the animals resemble human patients. There is a difference in that the functional overstrain in dogs results in actual anatomical destruction of cells in the islands of Langerhans, while such an anatomical effect in human patients is still doubtful.

The rôle of fat in diabetes will be discussed in its relation to three subjects.

I. LIPEMIA.

The first of these is lipemia. Here we deal with the disposal of fat from its absorption by the bowel to its taking up by the cells of the body. A few words may be devoted to the normal process, which is still obscure in essential points. An early dispute concerning digestion has been settled, since it is established

that fat is not absorbed in emulsion as such but only as the split products. In the intestinal epithelium the glycerin and fatty acids are recombined into neutral fat. Some earlier researches, especially those of Rosenfeld and others in the dispute over fatty degeneration and infiltration, led to the view that this recombined fat is identical with the food-fat; that is, that only the fat synthesized from carbohydrate or other foods can be peculiar to the species, while otherwise the fat of the body takes its character from the fat of the food. A series of authors, Bloor being the latest, have modified this extreme view, and have shown that the epithelium changes and rearranges the constituents to considerable extent, so that the recombined fat differs from the food-fat in being more nearly like the natural fat of the animal. The procedure of splitting and recombination therefore apparently serves for the absorption of useful fats, the exclusion of non-saponifiable substances such as mineral oils, and the partial modification of the absorbed fat to resemble the specific body-fat. Some of this recombined fat is perhaps taken up in the blood capillaries and carried in the portal circulation to the liver. But at least 60 per cent. of it is known to enter the lacteals and pass in fine emulsion through the thoracic duct into the systemic circulation. Obviously, it canot linger long in the blood, which would be hopelessly overloaded by the fat of a single meal. The cells remove it rapidly, so that, nothwithstanding the heaviest intake, the blood-fat like the blood-sugar varies only within narrow limits. In the phraseology of Magnus-Levy, the level of the blood-fat must represent the balance between inflow and outflow at any given time. This brings us to the consideration of the fat content of normal blood.

There have been described three physical forms in which fat may exist in the blood. First may be mentioned the occult form, which ordinarily predominates. The fine emulsion of the chyle is changed as it enters the blood stream. The droplets apparently dissolve, so that the clear blood plasma contains fat which cannot be colored by osmic acid or any fat stains or extracted by ether or other solvents, and can only be demonstrated by digesting the proteins with enzymes, acid, or alkali, or precipitating them with

reagents such as alcohol. This fat is probably non-dialyzable and seems to exist in some colloid combination. The second form consists of surplus or less soluble fat, in microscopic droplets, the blood-dust or hemoconia. These can be stained with fat stains and extracted with fat solvents, and as they increase they make the plasma first turbid and then milky, as in digestion lipemia. The third possible form of fat is perhaps never normal. It is the form described by several authors when the plasma is cloudy or even opaque, yet cannot be cleared by the centrifuge; tiny droplets may or may not be visible under the microscope, but the substance is not colored by fat stains or dissolved in ether or chloroform. Boggs and Morris reported over 4 per cent. of this form of fat in the blood in anemic lipemia of rabbits. Bloor found that this form arises *in vitro* when certain abnormal (viz., diabetic or anemic) bloods are allowed to stand, the previously clear plasma becoming turbid. The three physical forms are presumably due to varying proportions and combinations of fats and lipoids among themselves, and possibly with proteins, salts, or other substances. Normal fasting plasma is clear and, according to Bloor, contains approximately 0.29 to 0.42 per cent. fat in human beings, and somewhat more, viz., 0.51 to 0.66 per cent. in dogs. Turbidity may appear within about an hour after a fat meal; it reaches its maximum in about six hours, and after twelve hours the plasma is again clear. The susceptibility to alimentary lipemia, in other words the balance between the digestive function and the assimilative function, differs in different species. Nothing is known concerning differences in the rate at which their tissues can take up fat. Rabbits are resistant to alimentary lipemia, and increasing the dose of fat merely causes diarrhea (Neisser and Bräuning). Sakai proved that rabbit blood has no unusual capacity for carrying concealed fat. Therefore it is possible to accept the explanation of Kreidl and Neumann, based on dark-field examinations of hemoconia, that intestinal absorption of fat is much slower in herbivora than in carnivora; but the question has not been investigated chemically, and offers a promising opportunity for the use of the new micro-methods. The goose has such a digestive power that it can be enormously fattened by

forcible feeding; and in the serum of such stuffed geese Bleibtreu, also Hervson and Sedel, found some 6 per cent. fat, though the rye used in Bleibtreu's feeding contained only 1.5 to 2.5 per cent. fat. Stuffing geese with fat-free food did not cause lipemia. Man and the dog are intermediate between these extremes. Alimentary lipemia between 1 and 2 per cent. is probably the highest that ever occurs in normal human subjects. Munk and Friedenthal found as high as 3 per cent. alimentary lipemia in dogs. It is impossible to produce in dogs a lipemia equal to that of the stuffed goose by any quantity or duration of fat feeding, for the digestion breaks down before any such plethora is produced in the metabolism.

Thus far the word fat has been used in the old-fashioned sense, indicating the whole of the ether-soluble constituents. But aside from the neutral fat, which preponderates, and the soaps and free fatty acids possibly occurring in small quantities, there are constantly present the substances called lipoids, grouped under the titles lecithin and cholesterol. Such phosphatids and sterols exist in every living cell; they are evidently of the most indispensable importance somehow, but their function is practically unknown. Even the gross metabolism of lecithin and cholesterol is mostly unknown. They can be absorbed as such from the bowel and also synthesized by the body. Cholesterol especially is excreted through the bile and feces. The nervous system is rich in these substances, and the liver, the red corpuscles, and the adrenal cortex have all been claimed to play a part in their metabolism. Bloor finds that the lecithin and cholesterol are each about a third of the total ether-soluble extract of normal blood. Their ratio is fairly constant and remains so in most pathological conditions, suggesting an important relationship. The quantity of glycerides in the fasting plasma might possibly be zero, which would mean that the entire transport of fat would be in the form of lecithin and cholesterol esters; but a small quantity of simple fat is probably present. Digestion of fat brings an increase in the glycerides.

Both lecithin and cholesterol rise in most forms of lipemia. Lecithin is markedly increased in alimentary lipemia even though

the ingested fat be practically free from lecithin. Terroine, Hagenau and others observed a similar parallelism between fat and cholesterol even when the food fat was extremely poor in cholesterol; and Sakai laid down the rule that there is no lipemia without cholesteremia, supposedly because of the solubility of cholesterol in fat; and Gardner and Lander have pointed to an absorption of cholesterol from the bile; but Bloor has found no change in the cholesterol during alimentary lipemia. The occurrence of the lipoids free or in esters or other compounds may have special significance, but this is unknown at present.

The relations in plasma and corpuscles also deserve notice. Normally, according to Bloor, lecithin and cholesterol are nearly equal in the plasma; the lecithin content of the corpuscles is approximately double that of the plasma, and also double the cholesterol of the corpuscles. Bloor assumes that two-thirds of the plasma cholesterol is combined in esters. It is believed that all the cholesterol of the corpuscles is free. The corpuscles contain no true fat or only indeterminable traces.

Connstein claimed that the presence of red corpuscles is necessary in order for the fat to be changed from the emulsified to the soluble form. Munk and Friedenthal asserted that the corpuscles actively take up fat, so that in alimentary lipemia they may contain a higher percentage than the plasma. Bloor has confirmed this statement, and furthermore has found that lecithin increases chiefly in the corpuscles and only slightly in the plasma. Following up the idea of Loew and of Leathes that all fat is utilized *via* lecithin, Bloor has set up the hypothesis that all or most of the absorbed fat must be taken into the corpuscles and converted into lecithin before it can be assimilated. He finds here an explanation of the arrangement whereby fat is led into the general venous circulation to be thoroughly mixed with the blood before being carried to the liver or any other capillary domain for assimilation. Since lecithin is increased in a brief lipemia, as during digestion, he assigns special importance to it in the early stages of assimilation; and as cholesterol is increased in lipemias of long standing, he ascribes importance to it in the later stages of assimilation of fat.

The actual mechanism by which cells take up fat is unknown. Authors from Hanriot to Rona and Michaelis, Caro and Sakai have undertaken to demonstrate a lipase function. The process in assimilation would thus correspond to that in digestion. But the alleged lipase is so feeble that its presence or activity is hard to determine accurately by titration, and recourse is had to delicate physicochemical tests with the stalagmometer. Also, it seems truly characteristic of the subject of diabetes that the attempt should be made to explain lipemia by diminution of lipase, disregarding the extreme diminution of lipase in diseases without lipemia, as reported, for example, by Bauer. The lipolytic enzyme of blood seems classifiable with the glycolytic enzyme as accidental and unimportant, and the notion of enzymatic digestion of fat in the blood plasma or at the cell boundary does not merit serious consideration. On the other hand the conversion of fat into the plasma-soluble form, through the process supposed by Bloor or any other process, appears as a significant phenomenon. All living cells contain a similar "masked" or combined fat, and the most plausible view is that fat passes through the cell boundaries in this colloid or soluble form. Taylor refers to this as the "metabolic" form of fat. Nevertheless, it must be borne in mind that we are dealing with hypotheses throughout, and that nothing is known positively concerning the means by which the cells take up fat from the blood.

Except after meals it seems probable that hyperlipemia is abnormal like hyperglycemia. A slight lipemia accompanying exercise was observed by Murlin and Riche. Bloor suspects that excitement may increase blood-fat as it does blood-sugar. Animals possessing stores of fat show a slight lipemia during fasting, supposedly because of increased transport of fat. Bloor's highest figure was about 0.9 per cent. Slight lipemia may occur in pregnancy, but according to studies by Klinkert and others, cholesteremia is the most prominent feature, and is responsible for the occasional xanthelasma and possibly related to the accompanying hypertrophy of the adrenal cortex. Just as hyperglycemia, so also hyperlipemia may occur in various metabolic disorders. It may be found in obesity, alcoholism, and nephritis. Chauffard

and Grigaut described hypercholesteremia in nephritis. According to Lauber and Adamuck, Zinsberg and Chauffard the white flecks in the retina in nephritis are largely accumulations of cholesterol esters, and (Borberg, Landau) cholesterol is increased in the adrenal cortex. The familiar accompaniments of nephritis, namely, atheroma of blood-vessels and the arcus senilis of the cornea, likewise represent deposits of cholesterol esters. J. Müller reported an unusual case of nephritis, with chylous hydrothorax, and the above-mentioned opacity of the plasma which cannot be cleared by the centrifuge or fat solvents or stained with fat stains. Here the blood contained over 3 per cent. total fat, and 0.6 to 0.8 per cent. each of lecithin and cholesterol. Cholesteremia and lipemia are present with icterus, gall-stones, and liver disease, as shown by Klinkert and Beumer and Bürger. Cholesterol is deposited in the xanthoma formations and the cholesterol content of the bile is said to be increased. Lipemia has also been reported in pneumonia, heart disease, dyspnea, syphilis, and esophageal cancer, some of these cases being perhaps mere alimentary or inanition lipemia. The lipemia in a number of other conditions named by Fischer is doubtful. Experimentally, slight lipemia occurs in poisoning with phosphorus, phloridzin, and other drugs causing fatty degeneration, and during and after narcosis, though the phenomenon is inconstant (Murlin and Riche, Bloor, Lattes and others). Fat emulsions injected intravenously are rather promptly disposed of by the liver and other tissues, and lipemia is resisted. Bloor's highest figure after such injections is 1.5 per cent. blood-fat. It is well known that intoxication with fatty acids has been suspected in the etiology of some clinical anemias. The analyses of Freund and Obermayer, Erben, and Beumer and Bürger show lipemia absent in pernicious anemia and some cases of leukemia, and in other cases of leukemia a slight lipemia up to 0.7 per cent. Bloor gives similar findings in pernicious anemia, with the suggestion that the low cholesterol values may be significant in view of the protective action of cholesterol against hemolytic agents. Boggs and Morris observed lipemia in a man with anemia secondary to hemorrhoids. They compared it with lipemia which they discovered in rabbits made anemic by re-

peated bleedings; they found no lipemia in cases of equal anemia produced by pyrodin poisoning. In the anemia of phenylhydrazin poisoning, Sakai described lipemia of approximately 1 to 3 per cent.; and as observed by Underhill, fatty liver and hypoglycemia accompany such poisoning. When the anemia was produced by bleeding, Sakai found values almost up to 6 per cent. blood-fat, with proportional increase of lecithin and cholesterol. These are the highest figures ever reported for non-diabetic lipemia.

We come now to the principal metabolic experiment which nature has performed for us, namely, diabetes. Just as there is no other way of producing hyperglycemia equal in intensity and duration to that of diabetes, so also the lipemia present in some cases of diabetes is beyond parallel in any other clinical or experimental condition. In blood taken from a thirteen-year-old diabetic child three days before death in coma, Frugoni and Marchetti reported a total ether extract of 27 per cent., and in blood from the same patient at autopsy 34 per cent. The highest figures fully accepted by German authors are 19.7 per cent. by Neisser and Derlin and 18.13 per cent. by B. Fischer. For comparison it is interesting to note that the highest known value for fat in thoracic duct chyle, by Zawilsky with maximal fat feeding in dogs, was only 14.6 per cent. Sakai reckoned that the blood in Fischer's case contained over 700 grams of fat. There are numerous reports of all grades of lipemia below this. Imrie has described one of the most recent cases, with over 14 per cent. fat in the blood. The most comprehensive chemical study has been made by Bloor, who gives complete analyses in thirty-six of Joslin's patients. He found the blood-fat normal or even subnormal in mild cases, but always increased in severe cases, ranging up to twice the normal. Two untreated cases showed the typical excessive lipemia, one with 2.9 per cent. and the other with 11.2 per cent. of fat in the plasma. Such lipemic blood looks like cocoa, and the plasma like cream. Tyson's 1881 text-book and Joslin's 1916 text-book both devote the frontispiece to lipemia, the latter showing the appearance of the blood and plasma, the former depicting the fundus of the eye, for the con-

dition is so marked that it can be recognized by intraocular examination. Normal urine contains a trace of fat, and this is increased in lipemia, Frugoni and Marchetti's case showing 0.088 per cent., Imrie's case 0.1 per cent., and Neisser and Derlin's case the unusual figure of 0.8 per cent. urinary fat.

For closer understanding, inquiry may be made first as to the nature of the fat circulating in such excess in these cases. Analyses from Fischer to Bloor show that the great mass of it is neutral fat. Klemperer and Umber's claim that both lecithin and cholesterol are increased out of proportion to the neutral fat and their suggestion of the name lipoidemia instead of lipemia have been overthrown by more recent work. The lipoids are increased, but the higher the lipemia the greater is the predominance of the true fat. Imrie agrees with some earlier authors in finding lecithin relatively low in diabetic lipemia. Bloor has shown that lecithin varies somewhat in parellel with the total fatty acids until marked lipemia is reached, then falls markedly behind in relation to both these and cholesterol. The striking increase in cholesterol has been noted by authors from Fischer onward. In Imrie's case the blood contained 1.5 per cent. cholesterol. Bloor's case with 2.9 per cent. lipemia had 0.5 per cent. cholesterol, and his case with 11.2 per cent. lipemia had 1.26 per cent. cholesterol. There is evidently a remarkable activity of cholesterol metabolism. The liver is generally bright yellow, but Fischer remarked that the liver cells did not contain large fat-drops as in ordinary fatty livers. The Kupffer cells like the endothelia elsewhere are stuffed with fat, and Kawamura found that this fat consists not merely of glycerides but cholesterol esters, which he claims the Kupffer cells normally refuse to take up. Jastrowitz undertook to study lipoid infiltrations in the fatty livers after various poisons. Beumer and Bürger described a case of diabetes in which an oat-cure cleared up the existing lipemia, but the cholesterol persisted at three times the normal figure. Klinkert states that the white spots in diabetic retinitis represent accumulations of cholesterol esters which may clear up considerably under treatment. The apparent thickening of the vessels of the fundus of the eye in lipemia is due to the opacity

of the plasma and also to the cholesterol ester infiltration of their walls. Xanthomata are an expression of hypercholesteremia in diabetes as in other conditions, though other factors must be concerned. Von Noorden saw them clear up under treatment and return with aggravation of the diabetes. Bacmeister in one case furnished rather doubtful evidence that the cholesterol excretion in the bile may be markedly increased in diabetes. Of other compounds it may be noted that Imrie reported 0.38 per cent. of fatty acids present in the blood as soaps. Aside from the anemia-producing effects, fatty acids and their soaps are highly toxic, Munk finding that 0.11 to 0.13 gram oleic acid as soap injected intravenously in thirty to forty-five minutes suffices to kill rabbits by heart-block. Lipemic patients show no more anemia or intoxication than other diabetics, so it would seem either the findings of high percentages of circulating soap are mistaken or other substances present must protect against its poisonous action. In survey, therefore, it may be said that diabetic lipemia is characterized by an increase of lecithin, which becomes relatively deficient as the lipemia becomes excessive; but comparison with other forms of lipemia is difficult, for it seems probable that if alimentary or any pathological lipemia could be raised as high as diabetic lipemia the relative deficiency of lecithin might be similar. Analyses on stuffed geese would be interesting. Diabetic lipemia is also characterized by a much greater increase of cholesterol, almost parallel with the fat, in excess of anything ever observed outside of diabetes, and in direct contrast to what occurs in alimentary lipemia.

Another contrast is seen in the corpuscles, for instead of the increase which occurs in alimentary lipemia, their fat content amid the tremendous lipemia of diabetes remains normal. Bloor finds the same to be true in other forms of pathological lipemia. The entire chemical picture is interpreted by Bloor as follows. The component which becomes more predominant as the lipemia increases is the true fat, which is the inert form of fat, and its accumulation indicates that the fat is not being properly prepared for assimilation. Likewise the relative deficiency of lecithin and the lack of fat in the corpuscles indicate that the

corpuscles are not performing their function of transforming fat into lecithin, as in the earlier phase of assimilation. The high cholesterol figures are taken to mean that a later stage of the process is represented in this lipemia and that the cholesterol mechanism has not failed. Beumer and Bürger concluded that a considerable part of the cholesterol is free and not in esters, and in Imrie's case practically the whole of the cholesterol was found to be free. This fact might be significant if generally confirmed. Throughout it must be remembered that the entire subject is in the stage of hypotheses, but they are interesting as such and represent a real beginning in attacking the problem.

A second point for inquiry is the source of the fat in lipemia. In alimentary lipemia it is sufficiently obvious that the fat is derived from the food, but the lecithin, aside from what may come from the food, must be supplied by the body. In the various forms of pathological lipemia, lecithin and cholesterol must presumably be supplied by the body; this was certainly true in Müller's case of nephritic lipemia, in which the patient had been on lipoid-poor diet for months. In the anemic lipemia of rabbits, Boggs and Morris showed that the tendency to alimentary lipemia was increased, but yet the essential source of the blood-fat was the body-fat, for the lipemia developed on a diet of bread and grass, the animals rapidly lost weight, and in extreme emaciation the lipemia ceased. Because of the high lipoid content in diabetic lipemia, Klemperer and Umber concluded that the condition represents an increased breakdown of body cells, since only these could furnish so much lecithin and cholesterol. This explanation seems foolish when applied to a lipemia of 10 to 20 per cent. Several authors have followed the hypothesis that the lipemia is derived from the body fat. Magnus-Levy has upheld the opposite view that the blood-fat is derived from the food, that the fat is taken up from the intestine and poured into the blood as usual, but there is some obstacle to its leaving the blood, either a physicochemical difference in the fat itself or a change in the cells or in the capillary walls; and that the huge quantities sometimes found in the blood may result from slow accumulation. Neisser and Derlin's patient with 19.7 per cent. blood-fat had very little

body fat. They compared the iodin and Reichert-Meissl numbers of the fats in the food, chyle, blood, and several tissues and concluded that the blood-fat comes from the food. Imrie considered that the 300 grams or more of fat in the blood of his patient was too much to be derived from the food; the iodin number of 73 for the fatty acids of the blood compared well with 68 for the adipose tissue, but differed widely from that found in liver, heart, and kidney; he therefore concluded that the lipemia represents mobilization of connective-tissue fat. Bloor observed extreme lipemia only in two patients who had been eating excessive amounts of fat, while severe cases under treatment with restriction of fat as well as other foods seemed to show the tendency but the figures were moderate. Accordingly, he considered that the lipemia is derived from the blood and is due to ingestion of fat beyond the capacity of a weakened assimilative function. It is to be regretted that very few fat determinations have yet been carried out on our patients at the Rockefeller Institute Hospital. The gross observations agree with the experience of Bloor and Joslin that even the most creamy plasma clears up under treatment. One extremely emaciated man showed a diminishing but still opaque lipemia through six days of fasting, which disappeared only gradually in the subsequent treatment. The exit of fat from the circulation must therefore be very slow in some cases. It should be considered a therapeutic duty to clear up a pathologic lipemia.

Dogs are subject to diabetic lipemia, as shown by an observation of Gerhardt mentioned by Naunyn, of 12.3 per cent. blood-fat in a dog with spontaneous diabetes and pancreas necrosis, which is the highest lipemia ever recorded in a dog. It is impossible for a dog to have more severe diabetes than that following total pancreatectomy, but the plasma generally is almost or quite clear. In an exceptional instance Seo observed lipemia of 2.4 per cent., with increase in lecithin and cholesterol. It is possible that Seo's dog was fat and that Gerhardt's dog had been eating fat. The facts perhaps indicate that the lipemia does not represent mobilization of tissue fat by the intense metabolic disturbance, unless to some extent in a fat-rich animal, but that on the

TABLE III.—DOG 345 (PARTIALLY DEPANCREATIZED).

Date.	Weight.	Blood.‡ Plasma sugar, %	Hb. %	CO_2 capacity, Vol %	Acetone, qual.	Lipemia, qual.	Total fat, plasma %	Urine.† Volume, c.c.	Acetone, qual.	Total acetone,* mgm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.	Dextrose, gm.	D : N ratio.	Diet. Remarks.
June 8	11.25	0.232	112	..	0	0	0.92	..	..	..	..	..	..	..	..	
9	..	..	..	..	0	++++	..	778	+++	43.6	6.900	..	..	70.79	..	
10	..	0.276	109	..	0	++++	3.88	880	+++	80.1	6.432	0.730	8.80	73.30	..	
11	..	..	..	..	..	..	..	835	++++	48.4	3.932	..	..	39.83	..	
12	10.5	0.228	110	..	?	0	2.42	562	+++++	25.9	3.844	0.612	6.26	43.27	..	200 gm. lung; 100 gm. bread; 100 gm. suet.
13	..	..	..	..	..	..	..	764	+++++	10.7	4.769	0.609	7.85	34.63	..	
14	..	0.213	108	50.0	+	+++++++	7.12	1270	..	58.4	5.092	0.531	9.58	65.65	..	
15	10.75	0.333	112	57.6	+	+++++	6.00	940	++	..	5.038	0.394	12.80	64.95	..	
16	..	0.313	106	..	..	+++++	2.27	985	..	.	9.600	0.610	15.72	61.56	..	
17	..	..	..	..	..	..	..	990	..	..	6.672	..	..	61.87	..	
18	..	..	..	..	..	..	..	732	..	..	4.721	0.490	9.65	48.82	..	
19	10.85	..	..	..	..	..	..	1180	..	94.0	3.327	..	..	49.08	..	
20	..	..	..	..	..	..	..	598	..	35.9	2.738	0.203	13.42	44.35	..	200 gm. lung; 100 gm. bread; 150 gm. suet.
21	..	..	..	..	..	..	..	1370	..	..	5.918	0.479	12.38	59.59	..	
22	..	0.244	90	..	++++	++++++	3.16	1810	+++++++	1042.6	5.249	0.796	6.60	78.73	..	Unwell.
23	..	..	..	..	..	..	..	1270	+++++++	812.8	6.731	0.792	8.50	68.58	..	
24	..	..	..	..	..	..	..	2090	..	1097.3	3.762	0.501	7.55	58.30	..	
25	..	..	..	..	..	..	..	915	..	657.8	6.405	0.602	10.66	67.71	..	
26	..	0.238	93	38.5	..	+++	3.79	590	+++++++	367.0	4.838	0.489	9.88	40.45	..	100 gm. lung; 100 gm. bread; 100 gm. suet.
27	..	..	..	..	..	..	..	804	..	313.6	3.939	0.426	9.26	64.32	..	
28	10.82	..	..	..	..	..	..	1285	..	..	4.011	0.552	7 26	75 68	..	Unwell.
29	..	..	..	..	..	..	..	620	..	282.7	2.852	0.303	9.40	47.74	..	
30	10.65	0.213	96	40.4	..	+++	..	690	+++++++	298.1	3.008	0.324	9.26	43 20	..	
July 1	..	0.222	97	..	++	+++	..	396	..	182.1	7.680	0.760	10.10	30.50	3.97	600 gm. lung. Improving.
2	..	..	..	..	..	..	..	608	..	307.8	12.800	1.137	11.21	35.90	2.80	
3	..	..	..	..	..	..	..	332	+++++++	127.2	8.370	0.713	11.78	23.90	2.86	
4	..	0.270	109	34.2	++	+++	1.53	636	..	359.3	16.250	0.850	19.11	30.60	1.88	
5	..	0.256	94	43.9	..	..	0.78	405	..	..	9.450	0.940	10.10	31.20	3.30	
6	10.3	0.323	90	36.1	..	0	0.90	830	++++	192.6	16.600	1.930	8.60	51.90	..	600 gm. lung; 100 gm. bread. Good condition.
7	..	0.250	86	39.1	+	0	..	728	+++++	180.2	9.770	..	..	47.10	..	
8	..	0.357	86	47.7	..	0	..	1585	++++	518.3	14.300	1.100	13.00	106.20	..	
9	..	..	..	..	..	..	..	1600	++++	488:0	15.400	..	..	94.40	..	
10	10.13	0.304	86	46.4	+	0	1.98	2025	++++	559.0	10.400	1.010	10.30	93.10	..	

* Total acetone bodies as acetone. † Not catheterized. ‡ Blood drawn twenty-four hours after feeding.

TABLE I.—DOG 396 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.‡ Plasma sugar, %	Hb., %	CO_2 capacity. Vol %	Total acetone,* mgm. per 100 c.c.	Lipemia, qual.	Total fat, plasma %	Urine. Volume, c.c.	Total acetone,* mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	D : N ratio.	Weight, kg.	Diet.	Remarks.
Aug.																
16–17	0.465	102	..	..	0	0.509	1313	761.6	50.55	24.10	1.97	12.25	2.10	..		
17–18	0.327	96	57.6	..	0	0.512	1358	614.8	59.70	22.80	..	..	2.62	11.16	1000 gm. lung.	
18–19	0.400	85	42.4	..	0	0.516	1430	344.9	58.40	25.40	2.58	9.85	2.30	10.90		
19–20	..	..	..	..	..	..	1290	443.8	71.50	22.60	1.74	13.00	3.16	..		
20–21	0.356	104	36.2	33.9	0	0.586	1220	873.5	67.20	23.80	1.83	13.00	2.82	10.80		
21–22	0.384	103	..	12.5	++++	1.752	410†	111.4	19.20	5.77	0.45	12.80	3.33	10.70		Eats entire diet taking suet first.
22–23	0.324	98	46.2	29.0	++++++	1.600	804	405.2	24.92	11.58	1.36	8.52	2.15	10.82		
23–24	..	..	..	..	..	..	985	425.5	26.35	11.20	1.88	5.95	2.35	10.86		
24–25	0.285	59	48.1	70.8	++++++	0.835	860	359.9	31.85	10.50	1.37	7.66	3.03	10.70		
25–26	..	..	..	..	..	..	915	786.9	19.08	11.30	1.10	10.30	1.68	10.80	400 gm. lung; 200 gm. suet.	
26–27	..	..	..	..	..	..	782	297.1	26.00	10.95	3.98	2.75	2.38	..		
27–28	0.268	39	32.8	97.8	+	0.445	1018	260.6	24.20	10.15	..	..	2.38	10.75		Growing weak; fatty diarrhea.
28–29	0.385	64	30.9	57.5	0	0.533	922	191.8	26.40	8.64	1.37	6.30	3.06	10.25		Diet forced; vomited; 5 gm. sod. bicarbonate.
29–30	..	..	..	..	..	..	720	123.8	30.00	10.30	2.74	3.76	2.91	10.20		
30–31	0.294	45	38.6	67.0	0	0.365	1020	..	24.40	9.50	4.40	2.16	2.57	10.17		
31–Sept. 1	..	..	..	..	..	..	938	..	24.10	6.60	3.00	2.20	3.65	..		Moribund; killed.

* Total acetone bodies as acetone. † Incomplete specimen. ‡ Blood drawn twenty-four hours after feeding.

TABLE II.—DOG 280 (SEVERE DIABETES).

Date.	Blood. Plasma sugar, %	Hb., %	CO_2 capacity. Vol %	Lipemia, qual.	Urine. Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	Sugar, gm.	D : N ratio.	Diacetic acid.	Remarks.
Aug. 11–12	..	..	..	..	3.07	0.930	3.30	6.35	2.07	+++++	Fasting.
12–13	0.345	70	24.2	+++++	15.21	3.66	4.16	37.92	2.50	+++++	
13–14	0.435	70	20.0	++++++	7.19	0.50	14.40	7.66	1.06	+++++	Bicarbonate. Death.

contrary it mostly represents deficient assimilation of fat, and that depancreatized dogs with their maximal diabetes show little lipemia because in them the deficiency in assimilation is balanced by the deficiency in digestion of fat.

This supposition can be tested in dogs of the type described at the outset, which have severe diabetes along with satisfactory digestive power. It is found that they are in fact subject to diabetic lipemia in its full intensity. These dogs have been fed suet, which is not the most easily or rapidly digested form of fat; but approximate determinations in our first case indicated lipemia rivalling that of Gerhardt. The tables show some values incidentally observed in connection with other work. Here is a sample of plasma from a child entering the Institute Hospital in coma. It contains 11 per cent. fat. The analyses made thus far show wide differences in the curves of fat in the blood of normal, phloridzinized, and diabetic dogs after identical feedings. The minor fluctuations will require further study, but the outstanding feature is the disproportionate increase in the diabetic animal. Granting severe diabetes, the lipemia varies largely with the digestive power. The record of dog 396 (Table I) shows how the lipemia fell as the digestive power failed and the plasma became clear. These figures represent analyses twenty-four hours after feeding. On withdrawing fat from the diet lipemia clears up in from one to several days, according to its intensity, as seen in dog 345 (Table III). A possible exception to this rule may occur in a type of fasting acidosis to be described later. In the terminal state of dog 280 here dipicted (Table II) gross observations gave the impression of an increase of blood-fat up to the development of a marked lipemia on fasting, but the opacity of the plasma was the only index, and this chance for a decisive verdict concerning the possible occasional origin of diabetic lipemia from body fat was lost through inability to carry out the necessary analyses.

The production of diabetic lipemia in dogs is a simple matter, but it opens opportunities. Here we have the means of flooding the body with fat in a manner unparalleled outside of diabetes, of making and unmaking this abnormality easily and quickly.

The first result is the conclusive proof that the lipemia is derived ordinarily from the food-fat. It will be a simple matter to feed a variety of fats and compare with the blood-fat in the different cases; some information concerning fat assimilation may thus be gained, and we may be able to report such experiments later. But the simple fact that the lipemia appears so readily on feeding fat and ceases so promptly on omitting fat suffices to settle the dispute concerning its usual origin.

It is expected to publish later some analyses of the lipoid content of the blood and various organs, but this phase must be omitted at this time. As far as comparison is possible between Seo's analyses of liver tissue in diabetic lipemia and those of Jastrowitz and others of fatty livers produced by various poisons, no indication is offered of any specific chemical character of the organ infiltration in diabetes. The huge amount of circulating fat and the remarkable activity of lipoid metabolism offer other opportunities which we shall not be able to follow up. The unusual quantities of cholesterol that seem to be formed invite a study of the excretion in bile and feces and other features important to those interested in cholesterol metabolism. Various problems lately under investigation by authors such as Aschoff, Landau, Mulon, and Borberg concerning the morphology and the chemistry of fats and the function of the adrenal cortex and other organs in regard to them may perhaps be studied with special advantage in a condition in which the lipoid metabolism is specially disturbed or exaggerated.

The metabolism of matter and energy has never been studied in human patients with extreme lipemia, and to avoid confusion from acidosis or other factors it is desirable to make a series of comparative observations on the same individual in the lipemic and non-lipemic condition, and this can be done most conveniently in animals. All are now familiar with the work in Lusk's laboratory, which has shown that the combusion of any food is increased as the supply of it to the cells is increased. Ingestion of any food increases the total metabolism more or less according to the kind and quantity of the food. Ingestion of fat causes alimentary lipemia and the combustion is preëminently of fat. Bleibtreu's

geese, stuffed with rye, with lipemia up to 6 per cent., are said to have shown respiratory quotients as high as 1.33. Whether the figures are strictly correct or not, it seems evident that values above unity were present, indicating combustion preëminently of carbohydrate and the formation of fat from carbohydrate. This means one of two things: either the carbohydrate or the general plethora inhibited the combustion of fat in spite of 6 per cent. fat in the blood—in which case Lusk's law of summation of stimuli is reversed—or if there was combustion of fat in the remotest degree proportional to the lipemia, the total metabolism or the formation of fat from carbohydrate must have been tremendous. Interesting modifications of this experiment might be made by giving fat-rich instead of carbohydrate-rich diet or by using partially depancreatized geese. It is well known that in diabetic patients or animals alimentary hyperglycemia is more pronounced than normal, but the effect on the respiratory quotient is less, and in severe cases may be absent altogether, and this is one of the best evidences of deficient combustion of carbohydrate in diabetes. The case with fat is different, for diabetic patients and even totally depancreatized dogs always burn fat readily. The distinction is not absolute, for depancreatized birds—chickens, ducks, geese—show intense hyperglycemia with little or no glycosuria and can even receive considerable carbohydrate by feeding or injection and dispose of it somehow. Their kidneys are highly impermeable to sugar, but there is a difference beyond this, for feeding or injection of sugar in severely diabetic dogs with renal impermeability means rapidly fatal hyperglycemia—possibly 2 per cent. blood-sugar. The diabetic birds do not metabolize their carbohydrate normally, for glycogen is deficient and emaciation and death occur. The mammalian kidney is almost impermeable for fat, so that lipemia cannot be checked by excretion; and the presence of acetone bodies indicates some abnormality in fat combustion. But the known abnormality consists merely in incompleteness in the end products; no experiments have ever indicated any difficulty on the part of the diabetic in attacking the fat molecule. Patients and suitable diabetic animals often go along on a certain level of marked hyperglycemia, without glycosuria,

and evidently burning some carbohydrate. They seemingly require a higher "pressure" of sugar in the blood in order to accomplish the combustion of sugar. In the moderate hyperlipemia ordinarily present in severely diabetic patients, Bloor saw evidence of a similar need of increased fat "pressure" in the blood in order for the cells to burn fat. There is opportunity to test this idea with respiration experiments. In contradiction to the prevalent belief of normal fat assimilation in diabetes, investigation will probably show that a certain level of lipemia does not have equal metabolic influence in non-diabetic and in diabetic lipemic conditions. It will very likely be found that the effect on the gaseous exchange is slower and of less degree in diabetic lipemia, corresponding to the known facts concerning hyperglycemia in the milder cases, so that an alimentary lipemia of 2 or 3 per cent. in a normal animal may represent a greater activity of fat metabolism than much higher blood-fat values in an animal with diabetic lipemia. Also, it may be found that the metabolic effect varies among diabetics in proportion to their susceptibility to lipemia, and conceivably may not be fully normal in any severe diabetic. Studies of this sort will throw light on the ability of the diabetic to attack the fat molecule; they may help to show why fat-feeding seems sometimes neither to strengthen nor build up a patient; they will indicate what significance may be assigned to lipemia in the question of metabolism in diabetes; and by completing the proof that lipemia is due to deficient assimilation rather than increased mobilization of fat (even if increased mobilization sometimes occurs), they may contribute an analogy in support of the dominant belief that the hyperglycemia is primarily due to deficient assimilation rather than increased mobilization of sugar.

Our investigation of lipemia by the use of diabetic dogs to date has dealt chiefly with the problem of the actual cause of it, its relation to other diabetic phenomena and to the internal function of the pancreas, and the information which it may furnish concerning the fundamental diabetic condition. Besides the origin from food-fat, certain other questions can now be definitely answered.

First, the visible fat is not in the abnormal form insoluble in ether. Seo found in his one case that the opacity was cleared by ether, and the same has been our experience.

Second, the power of plasma to hold fat in clear solution is not diminished. In connection with the hypothesis of combined sugar, I formerly suggested a possible analogy with fat, in that lipemia might be due to deficient combination of the fat, and raised the question whether the pancreas supplies anything of importance for this combination. Reicher determined the fat before and after digesting blood with pepsin-hydrochloric acid, and concluded that the latter fraction has no importance. Seo mentioned visible lipemia in only one of his depancreatized dogs, yet the blood-fat in the other instances was from 1 to 1.5 per cent. This might indicate an unusually high power of the plasma to hold invisible fat, and the same possibility seems indicated by some of our experiments, and would not be surprising in view of the high lipoid content. Accordingly, no significant reduction in the simple ability of the blood to "mask" fat has been demonstrated. On the other hand, Bloor's belief is that fat must be combined into lecithin in order to be assimilated, and that a deficiency of this combining function is present in diabetic lipemia. The facts at least suggest that methods used for testing the combination of either fat or sugar should not be too crude.

Third, the relation of fat in plasma and corpuscles is of interest especially in connection with Bloor's hypothesis. Unfortunately most of our determinations so far have had to be limited to the plasma, and only a few analyses of corpuscles have been made. Thus far they indicate low total fat content in the corpuscles. Having controllable experimental conditions, it should be possible to trace any significant alterations from the normal through the mildly lipemic animals to the extreme degree in the severely lipemic animals. This research is in progress, but it is better to omit discussion at present rather than attempt conclusions from insufficient data.

Fourth, lipemia is not due to hyperglycemia. For example, mildly diabetic animals, even with abundant fat in the diet, may

be made to show extreme hyperglycemia without corresponding lipemia.

Fifth, lipemia is not due merely to absence of carbohydrate or loss of sugar from the body. Maximal phloridzin poisoning with feeding of nothing but fat, or the longest possible phloridzination on diet free from carbohydrate and high in fat, has failed to produce in dogs anything resembling diabetic lipemia.

Sixth, lipemia is not due to the presence of acetone bodies. Lipemic patients generally have acidosis, but a case of lipemia without ketonuria was described by Beumer and Bürger. It is well known that many patients with severe acidosis and even coma show clear plasma. Bloor found "no definite relation between high blood lipoids and the occurrence of acetone bodies in the urine." In dogs it can be shown that the acidosis of phloridzin poisoning causes nothing like diabetic lipemia, that diabetic acidosis may occur without lipemia, and that marked lipemia may be present without acidosis. Maximal lipemia probably never exists without acidosis, but this is because acidosis goes with the general severity of the diabetes.

Seventh, lipemia is not due to change in the reaction of the blood. The greatest possible reduction of the carbon dioxide capacity by diabetes, phloridzination, or chronic hydrochloric acid poisoning has produced none of the characteristic lipemia.

Eighth, lipemia is not due solely to removal of pancreatic tissue within the limits mentioned. If enough pancreatic tissue is removed to produce even severe diabetes, but the actual occurrence of diabetes is avoided by diet, the characteristic lipemia does not occur. In some such cases alimentary lipemia certainly persists longer than normal, but this may represent merely a slower digestion of fat owing to the smaller supply of pancreatic juice. If the curve of the lipemia is lower as well as longer, it will indicate such delayed absorption. The characteristic of diabetic lipemia is that it both rises higher and falls more slowly than normal. When the assimilative disturbance is slight it may to some extent be balanced by the delayed absorption, so that the mere prolongation of slight lipemia becomes hard to interpret. These experiments are in progress and a sufficient number are

not yet finished to permit positive conclusions. But it is certain, as stated, that the full diabetic lipemia never occurs in the absence of other symptoms of active diabetes.

Ninth, lipemia is not the result of breaking down of a hypothetical "fat function" by direct overstrain of that function. Here again tedious experiments extending over months have been involved. These experiments have proved that the heaviest and most prolonged fat diets, in normal and partially depancreatized animals, neither increase nor diminish the susceptibility to lipemia. If the conditions are such that the fat-feeding gives rise to glycosuria and acidosis, the lipemia begins to mount up; otherwise not.

Tenth is the question of the relation of lipemia to the severity of the diabetes. Up to the time of the present treatment which restricts fat in the diet, high lipemia has been considered a sign of very bad prognostic import. Bloor found some elevation of blood-fat in all severe cases, normal or subnormal values in mild cases. Beumer and Bürger have reported the only known instance of lipemia in mild diabetes. In dogs of the type described above, it is easy to show that the lipemia depends upon the severity of the diabetes. The partially depancreatized dog, with relatively little tendency to lipemia as long as he is kept free from diabetes, acquires the marked susceptibility without any further operation as soon as severe diabetes is brought on by overfeeding with any kind of food. The most striking experiment is to keep the plasma continuously clear by carbohydrate or protein diet, then suddenly give a meal of fat. High lipemia is present within a few hours and persists for more than twenty-four hours. On continuance of fat diet the lipemia mounts to a point governed by the digestive power. As in human cases, it is then unremitting, and like an old hyperglycemia, varies relatively little with meals. With breakdown of digestion, or on withdrawal of fat from the diet, the lipemia clears up in from one to several days, according to its intensity. The tables already referred to illustrate some of these statements.

This permits discussion of the relation of lipemia to the internal pancreatic function. There may be three possibilities: Is

lipemia due to disorder in some organ or in the general system secondary to the original diabetic disturbance? is it another manifestation of deficiency of the same hormone concerned in carbohydrate metabolism? or does it represent lack of some different internal secretion of the pancreas? There is sound justification for speaking of several internal functions of the pancreas. Diabetes is not a mere glycosuria or inability to assimilate glucose. There are abnormalities in the metabolism of protein, fat, and doubtless of mineral substances, which are primary and cannot be reproduced secondarily by phloridzin or any other means. But it is possible that the various functions in question all belong to one internal secretion, and this unitarian hypothesis is inherently the most attractive one. It is a plausible view that the pancreas supplies something necessary for the synthesis and maintenance of protoplasm, that deficiency of this factor makes nutrition of the cells difficult and disposes to breaking down of their reserves, and that this tendency makes itself felt in regard to all classes of foods, but earliest and most manifestly in regard to the most labile and most easily excreted forms. Only positive evidence could justify a doctrine of plurality of internal secretions of the pancreas. The unitarian standpoint would have theoretical importance, for it might reasonably be inferred that the part played by the single hormone would be similar toward the various classes of foods. Glycosuria and non-assimilation of carbohydrate—lipemia and acidosis—increased protein catabolism, aminosuria, and changes in the creatin-creatinin relation—diabetic edema and other anomalies concerning salts—all afford different lines of approach. If all alike are due to deficiency of a certain action of a single hormone, comparisons will aid in learning what the action of this hormone is, and by following the different trails it may be possible to track the thing home and master the secret of the internal pancreatic function and diabetes.

Between the partially depancreatized animal without diabetes or lipemic tendency, and the same animal after feeding has brought on severe diabetes and susceptibility to lipemia, there is only one known anatomical difference, which consists in exhaustion and degeneration of cells in the islands of Langerhans. The

fact that this alteration and the lipemic tendency come on simultaneously, and are typically produced by pure carbohydrate or protein feeding, proves conclusively that the disorder underlying lipemia is bound up to considerable extent with the other diabetic disturbance and is not entirely independent. Possible evidence for the existence of more than one internal pancreatic secretion might be found in the discovery of Lane and Bensley that the islands of Langerhans consist of two different varieties of cells, filled with granules which stain differentially; these cells are believed to be independent in origin and type and not transitional or derivable one from the other. This histological interpretation is strengthened by Homans' discovery that only the so-called Beta cells ordinarily degenerate in experimental diabetes, while the Alpha cells remain preserved even in advanced stages and show particularly dense granulation. This observation was confirmed in the work at this Institute. But it might still be possible that both types of cells are concerned merely in carbohydrate metabolism. Krumbhaar published the description of an important case of spontaneous diabetes in a dog, in which the pancreas was about twice the normal size and its tissue appeared normal; and microscopic examination showed advanced degeneration of the Beta cells everywhere, along with less extreme but still marked exhaustion of the Alpha cells. Lipemia or acidosis was not found in this animal, but it apparently was not studied on fat diet. Martin has discovered that some of our experimental dogs show this same degeneration of the Alpha cells. He is following up the investigation, but there has not yet been time for enough comparisons to establish the possible significance. When a dog shows a dextrose-nitrogen ratio equal to that following total pancreatectomy, it will be interesting to know whether the Alpha cells are degenerated or not. If they are intact their part in carbohydrate metabolism will become very questionable. Material is available from animals of different species, different ages, different grades of intensity and duration of diabetes, on various diets, in nutritive states ranging from obesity to emaciation, with lipemia and acidosis present or absent, and with other physiological or pathological variations, so that it may be possible to

throw some light on the function of the Alpha cells and the unity or plurality of the internal pancreatic secretion.

The facts concerning human patients must also be considered in this connection, and the question whether the full conditions are reproduced in dogs. Granting that all patients with severe diabetes have some tendency to lipemia, is this tendency equal in all of them? When the majority of cases show fairly clear plasma, and a small minority show lipemia of 10 to 20 per cent., can it be maintained that varying quantities of fat in the diet suffice fully to explain such differences? If there is another cause for the discrepancy, does this cause consist in some additional pancreatic disturbance, or in a breakdown in some other organ or in the general system? It is unfortunate that accurate observations covering this point have not been made; but probably most physicians who treat diabetes will have the decided impression that individual variations exist, and that the majority even of severe cases on heavy fat diet are not subject to the most intense lipemia. Though it is difficult to gauge the true severity of diabetes, possibly Beumer and Bürger's patient above mentioned manifested a special susceptibility to lipemia in the presence of only mild diabetes. Several of the patients at the Institute have shown intense lipemia, and it is not evident that their condition was more severe or that they had eaten more fat than some others without lipemia. Certain patients under treatment were tested with heavy fat diets for other purposes and remained free from lipemia. On the other hand, a very few incidental observations seem to indicate that when there has been heavy lipemia, and when it and the glycosuria have been recently cleared up, a meal of fat may cause the plasma to remain turbid for more than twelve hours. The suggestiveness of these chance observations is strengthened by the experience with dogs, in which such a phenomenon certainly occurs. It may prove worth while to investigate whether patients react differently to such a test and whether it signifies a specific weakness of fat assimilation.

Certain observations seem to indicate that in dogs the tendency to lipemia may vary independently of the other diabetic symptoms, and that the governing conditions are at least in part

experimentally controllable. The work in progress must be carried further before it will be possible to decide positively concerning such observations or interpret their significance for the theory of diabetes. The gist of the matter to date is that diabetic lipemia has been reproduced in dogs, and there are hopes that the possible varying grades of susceptibility shown by human patients may be experimentally imitated.

II. ACIDOSIS

The second subject for discussion in connection with the rôle of fat in diabetes is acidosis. Here the primary requirement for clearness is a definition, and the one adopted may be said to rest on three bases.

The first of these is origin and general usage. The pioneer workers of the Naunyn school grasped this problem broadly and deeply; they did the principal work that has been done, and they marked out the fundamental lines which all subsequent research has followed. Hallervorden recognized the significance of the increased ammonia. Stadelmann attributed coma to acid and suggested alkali therapy; it is noteworthy that he used in this connection the term acid intoxication, not acidosis. Minkowski perceived the presence and meaning of the diminished carbon dioxide content of the venous blood. Magnus-Levy determined the balance of acids and bases in the urine. But Naunyn introduced the term acidosis, and said, "With this word I designate the formation of β-oxybutyric acid in metabolism." The name and definition received general adoption, and have been used also by the opponents of the Naunyn school who believe that the intoxication and coma represent something other than a simple shift of reaction. The more recent followers of Naunyn should not pervert his definition, which has been acceptable to both parties; and even if the word must become the exclusive property of either faction, it is not for the losers to carry off the nomenclature.

The second basis of definition is that of need and distinctiveness. Diminished alkalinity, increased hydrogen ion concentra-

tion, lowering of carbon dioxide, decrease of buffer salts, and (for the symptoms of these changes) acid intoxication—all these terms have definite meanings, and to appropriate the name acidosis for any one of them is merely to create a useless synonym. No other name but acidosis exists for the metabolic process which it denotes. Ketonuria and ketonemia have their accurate place but do not cover the ground. Possibly the word ketosis might be suggested and used for special purposes, but the change of established usage would be difficult and seems unnecessary. It may be urged that there are states of increase of other acids, lactic, phosphoric, etc. If desired it may be feasible to include these under a broad interpretation of acidosis, and to distinguish them when necessary from acetone body or diabetic acidosis. But the latter is the original and most important type, and the name acidosis belongs preëminently to it.

The third ground for the definition is its fundamental significance. Here may be seen the sound judgment of Naunyn in defining on the basis of metabolism, not of reaction. A definition must be qualitative not quantitative. Criteria of reaction vary with the tests; the finer methods of today reveal changes not formerly perceptible, and future technic may give truer appreciation of the physiological balance in the blood or may follow changes into the cells. But the metabolic disturbance in question is continuous and must be regarded as a unit. It is recognizable at a time when the protective mechanisms of the body are apparently efficient to prevent any abnormality of reaction, and it persists in spite of any dosage of alkali. Furthermore, a comparison with typhoid fever is illustrative. Fever is a prominent feature in typhoid infection and has been embodied in the very name of the disease. Also, simple hyperpyrexia is a possible cause of death, and rightly or wrongly many physicians believe that they benefit patients and even save lives by treating this symptom with cold bathing or other measures. Nevertheless, the proper definition of typhoid fever must be in terms of infection with Bacillus typhosus and not in terms of fever. Similarly, the acid character of the products in acidosis is important and has received recognition in the name of the condition. Simple dis-

placement of reaction may be a cause of intoxication and even death, and clinical improvement and even the saving of life may be achieved temporarily by the mere administration of alkali. But the metabolic disturbance back of it all is the real thing to be defined and comprehended and treated. A slight objection might conceivably be raised on the basis of rare cases of reported coma without acetone bodies. But there is the old-time answer that such cases though occurring in diabetes may not be diabetic coma; and there is no evidence that a definition based on reaction would fit them any better. For these reasons it seems best to retain the definition of acidosis in the original sense of Naunyn—namely, as that state of metabolism of which the presence of abnormal quantities of the acetone bodies is the one known constant characteristic.

This leads to the question of the origin of the acetone bodies. Their appearance was first ascribed to fermentation of carbohydrate, then to breakdown of body protein. More recent experiments with phloridzin and liver perfusions prove the possibility of a partial derivation from the leucin, tyrosin, and phenylalanin of the protein molecule, while the greater portion of the amino-acids form glucose, and the exact status of some of them is uncertain. But the work of Rosenfeld, Hirschfeld, Geelmuyden, Magnus-Levy and others made it apparent that the principal source of the acetone bodies is fat. The disposal of fat up to the point of its leaving the circulation and entering the cells was discussed under lipemia. Aside from storage, its fate in the cells is supposedly combustion proceeding through successive carbon groups, the best accepted chemical view being the beta-oxidation hypothesis of Knoop, according to which butyric and β-oxybutyric acid may be normal intermediary products and excretion of the latter may represent merely imperfect combustion. One molecule of higher fatty acid could thus furnish only one molecule of β-oxybutyric, and Magnus-Levy calculated that the quantity thus available corresponds to the maximum known excretion, but that in some cases this demands a molecule of acetone bodies from practically every molecule of fat burned. Acetone is a secondary and chiefly abnormal product, but there is a question

which of the other bodies is primary. Formerly, diacetic acid was believed to be derived from β-oxybutyric by oxidation, but Maase, Blum, Dakin, and Marriott have brought evidence that the reverse may be true, and that diacetic acid may be the primary product formed from butyric, and β-oxybutyric be derived from it by reduction. The orthodox belief is that all cells, including muscle cells, burn fat directly. Von Noorden is one of the very few who imagine that the muscles can burn only sugar, which the liver forms from fat for their use, and that acetone body production is associated with the formation of sugar from fat. It is a common belief that the acetone bodies are produced largely or chiefly in the liver. In Embden's laboratory, perfused livers have been shown to form acetone, while kidney, lung, and muscle formed none; furthermore, the livers of depancreatized and phloridzinized dogs formed several times as much acetone as those of normal dogs. Also, Fischler and Kossow phloridzinized Eck-fistula dogs and found that these animals, with ligation of the portal vein and drainage of the portal blood directly into the vena cava instead of through the liver, showed less ketonuria than ordinary dogs likewise receiving 1 gram of phloridzin daily; but with the reversed Eck-fistula, that is, with ligation of the vena cava and drainage of its blood together with the portal blood through the liver, the ketonuria was increased above that of the controls. The experimental evidence thus seems strong, but it requires criticism. It would be well if more work were done along the lines of Fischler and Kossow, to learn whether their results are significant or accidental or whether any other conclusion is possible. Too much importance must not be attached to perfusion experiments or to the milligrams of acetone formed. It may well be conceded that liver cells are able to form acetone, also that acetone formation is more active in depancreatized and phloridzinized than in normal animals. But the negative experiments with muscle and other organs do not prove that they are unable to form acetone bodies or that the quantity which they form is small. For example, authors have reported that the liver perfused with glucose forms glycogen, but no one has demonstrated the formation of glycogen when

muscles are thus perfused, and it is certain nevertheless that muscles in the living body form much glycogen. The function of the liver is primarily metabolic; perhaps for this reason it gives more positive results on perfusion than other organs in which the metabolic is subsidiary to other functions. At any rate, the reason for the close scrutiny of these experiments lies in their disagreement with the chemical views of fat metabolism above mentioned. It would seem that only in the tangled field of diabetes could writers put together such doctrines as the predominant production of acetone bodies in the liver and the chemical views of Magnus-Levy and Knoop, with no consciousness of conflict. If there is anything like the excretion of one molecule of acetone bodies corresponding to each molecule of fatty acid burned, and if it be claimed that any large proportion of the acetone bodies arises in the liver, it follows either that the liver is burning this same high proportion of the fat, or else that the muscles are burning part of their fat perfectly while the liver is breaking up individual fatty acid molecules into several molecules of acetone bodies. Von Noorden's hypothesis is at least consistent on this point. But if, according to the accepted belief, cells in general attack the fat molecule directly, then acetone bodies are formed where the combustion occurs. In Woodyatt's metaphor, the engine "smokes" with acetone bodies. And since the great preponderance of combustion is in the muscles, it follows that the predominant formation of acetone bodies is in the muscles. The only escape would be in an improbable assumption that the muscles burn fat to a certain point and that hypothetical products are conveyed from them to the liver to be formed into acetone bodies. The proof for the chemical theories is not absolute, but it seems stronger than that for the origin of acetone bodies in the liver. Therefore, the most probable view at present is that the formation of acetone bodies takes place mainly in the muscles and other organs and only to a minor extent in the liver.

It is impossible in the present space to review the literature of acidosis or even the literature of fat-feeding, which more directly concerns the present topic. It is well known that fasting human beings regularly show ketonuria. It is not generally appreciated

how widely this phenomenon varies even in supposedly normal persons. Waldvogel and Brugsch observed instances in which fasting produced only trivial acetone excretion. Benedict's fasting man, eliminating approximately 2 to 7 grams of acetone bodies daily, may be considered a fair average. The upper extremes are represented in reports by Von Noorden of excretion of 48 grams in three days of fasting by a girl with gastric ulcer, by Bönniger and Mohr of excretion of over 24 grams in one day by a fasting woman, and by Gerhardt and Schlesinger of 40 grams daily in hysterical vomiting. The available store of body fat is one important factor, and Folin and Denis published a recent illustration of marked acidosis with symptoms in fasting obese women. But it is not certain that this is the sole variable, and only a large statistical study could show whether normal persons of similar nutrition have inherently different susceptibilities to acidosis. Ketonuria likewise results from simple carbohydrate abstinence, and fasting ketonuria is increased by protein-fat diet. Protein is considered antiketogenic in normal persons, the glucose-forming amino-acids prevailing over the others. Evidence that it may give rise to ketonuria has been offered by Rosenbloom and Hurtley for diabetic patients and by Kirk for depancreatized dogs. Such an effect is possible through loss of the carbohydrate portion leaving the ketogenetic portion, through a simple stirring up of metabolism and elimination (just as a submaximal D : N ratio in a fasting depancreatized dog may rise to maximal on feeding), and, in human patients, probably through aggravation of the essential diabetic process. In line with this, a high protein diet is inadvisable for the average patient threatened with coma. Fat constitutes the essential dietary cause of ketonuria in normal persons; for example, Landergren and Forssner thus produced excretion of some 40 grams of β-oxybutyric acid. Attempts have been made to establish the quantity of carbohydrate requisite to prevent acidosis, the figures generally being set at 50 to 150 grams. Geelmuyden found that more, perhaps 200 grams, might be necessary to abolish an existing acidosis, also that the quantity required varies with the quantity of fat in the diet. Zeller worked out a law that for prevention

of acidosis one molecule of sugar must burn for each two molecules of fat, which means the ingestion of one part of carbohydrate for four parts of fat. Von Noorden and his followers have emphasized the wide discrepancies between different diabetics as respects the relation between carbohydrate assimilation and acidosis: for example, Mohr's comparison between two patients under similar conditions, one of them excreting less than 1 gram of β-oxybutyric acid and the other over 15 grams, and his records of other patients with abundant ketonuria while assimilating 120 to 150 grams of carbohydrate. But Mohr mentions a similar discrepancy between two non-diabetics, and Forssner excreted 33 grams of β-oxybutyric acid with 40 grams of carbohydrate in his diet. Gigon tabulates the Landergren and Forssner experiments to show that individual idiosyncrasy is as marked among non-diabetics as among diabetics. It is well recognized, as shown in experiments of Reich quoted by Rosenfeld, that an initial ketonuria generally diminishes on continuance of the same diet. This behavior of normal persons is usually shown by diabetics who do well, and Mohr states that obese persons respond similarly. Folin and Denis observed that repeated fasts in obese subjects produce, so to speak, an "immunity" against acidosis, and the same has been noticed a number of times in our diabetic patients. A minority of diabetics develop serious acidosis on fasting, but when a short period of suitable diet, even protein-fat diet, is interposed, no case has yet been encountered in which a second fast was not well borne. On the other hand the Landergren-Forssner experiments give no indication of any such "immunity" to excessive fat diet. The great lack is of normal data. The Eskimos are much talked about but have never been studied. It is really unknown to what extent the normal human organism can accommodate itself to fat combustion or what proportion of protein or carbohydrate is the minimum necessary permanently to prevent acidosis. Some interesting acetone and ammonia figures ought soon to become available from severely diabetic patients who are kept free from glycosuria for long periods on diets low in protein and carbohydrate. The fat tolerance in such patients seems to differ widely. The susceptibility to acidosis

may perhaps also be governed partly by variables such as the age or the level of nutrition, whether high or low. Even under identical conditions the attempt to establish a universal rule on this point promises to be fruitless, for the reason that the widespread belief regarding acidosis as governed solely by a supposed ratio between fat and carbohydrate in combustion is incorrect. The existing evidence against it may be summarized as follows: (1) the seemingly constitutional idiosyncrasies manifested by both diabetic and non-diabetic individuals, shown in the literature; (2) the acidosis in certain infections, intoxications, liver necroses, and in the cyclic vomiting and gastro-intestinal crises studied by Howland and Marriott and others, in which deficiency of carbohydrate seems an inadequate explanation; (3) the acidosis which Taylor produced in himself by an ash-free diet of seventy-odd grams of protein, 120 grams of fat, and 200 grams of sugar. It is well for those who think of acidosis as necessarily due to lack of carbohydrate to bear in mind this well-authenticated case in which it was produced by lack of salt on a diet adequate in protein, moderate in fat, and liberal in carbohydrate. Rumpf and Joslin's idea of the importance of salts for threatened coma may find an analogy here. The fact that salt starvation has not had this effect in other such experiments perhaps adds to the evidence of personal idiosyncrasy. The experiment might bear repetition in subjects presumably disposed to acidosis, as the obese.

Notwithstanding that fat ingestion has been proved to create or increase ketonuria in both normal persons and diabetics, fat has remained the one unrestricted food in diabetes. Even Forssner saw reasons to justify the prevailing treatment, considering that tolerance for fat is acquired, that its addition to protein then increases ketonuria by only a few grams, and that its use is preferable to undernutrition. Naunyn, von Noorden and all others have agreed that fat should be withdrawn only in the presence of threatened coma. The few writers who have advocated occasional restriction of fat have merely favored limiting it to the caloric requirement of a maintenance diet. The more common practice has been to push fat by all possible devices

to the utmost limit of the digestive power, with the idea of building up strength and nutrition. Another support for the fat diet was given in the statement that the heaviest fat feeding only slightly increases the combustion of fat, the surplus being stored. In this connection the question arose why then ketonuria should be increased by fat ingestion, and various authorities inclined to the view that food-fat may somehow behave differently from body fat in metabolism. Murlin and Lusk proved that six hours after taking 75 grams of fat, a dog's heat production may be 30 per cent. above the basal. The protein-sparing power of fat is known to persist in diabetes. Therefore the absolute and relative increase in fat combustion now appears a sufficient explanation of the slight increment of ketonuria following any single fat meal, and the summation of such effects presumably accounts for the results of longer feeding, so that there is at present no evidence of a metabolic distinction between food fat and body fat. The relief of diabetic acidosis by fasting is doubtless due not only to diminished combustion of fat but also to a beneficial effect of undernutrition upon the assimilation of all classes of food. The fact that patients with severe diabetes frequently become almost free from acidosis, under the circumstances which give rise to a very appreciable acidosis in normal or mildly diabetic persons, would not appear so paradoxical if we had adequate information concerning the reactions and accommodations of normal subjects under truly comparable conditions. The diabetics merely demonstrate a reserve power in the human organism which normal persons could doubtless bring forth under an equal stimulus. Typical of the former treatment of diabetes has been the period when the patient was evidently developing this power and becoming able to live on protein-fat diet with little or no ketonuria; then the later period with heavy ketonuria, whether sugar-free on strict diet or glycosuric on mixed diet, and the necessary end in coma. The moral is that the natural or reserve powers of assimilation should be protected in treatment and should not be broken down by overfeeding with fat or any other food. The material for clinical experiments heretofore has comprised either fairly mild cases or severe cases with the usual heavy and fluctuating ketonuria. The

tests under these conditions have failed to reveal the insidious and cumulative injury caused by fat. When severe cases are made free from glycosuria and ketonuria, a material is afforded upon which any careful clinician can convince himself of the harm of excess of fat. Washing butter to remove traces of lower fatty acids while overwhelming the system with fat which must necessarily be katabolized into lower acids is one of the absurd practices of past treatment now abandoned. And finally it is to be noted that severe cases kept alive for months or years on low protein and carbohydrate, with glycosuria and acidosis kept up essentially by fat, are the cases that offer the greatest difficulty for successful treatment or for building up a tolerance for any kind of food.

It is important to extend research on acidosis to species other than man. A really satisfactory reproduction of the human condition is one of the greatest needs, for the very sake of the knowledge of how to produce it, and also for the opening up of a subject which always comes when it is made susceptible to animal experimentation. It is also desirable to study this disorder in species which do not so closely imitate man, because in man certain features are found quite regularly associated, and are generally conceived as belonging together, and it is valuable to learn whether this association is inevitable, and if not, to take such an opportunity to study the individual factors thus separated. There is no known laboratory animal which reacts precisely like man in this respect. Some apes or monkeys may be expected, according to Baer's findings, to show fasting ketonuria; but the large ones are too scarce and expensive, the smaller ones lack stamina, and it is doubtful if any of them can meet the requirements of appetite and digestion. Other species, as a rule, show ketonuria neither on fasting nor on protein-fat diet. A distinction is generally held between carnivorous and other animals, presumably on the assumption that animals accustomed to carbohydrate will have difficulty in burning fat without it, and on a vague generalization of the observations that dogs and cats are less easily subject to acidosis than man. The first thing learned in studying a variety of species is that this distinction

is wholly mythical. There are differences between species but none between classes of animals. Baer observed that herbivora are as immune to fasting ketonuria as the carnivora. He reported ketonuria in a pig on fasting but not on protein-fat diet. A pig which we studied at the Institute proved more resistant to ketonuria than any dog; and persons who may have cherished a secret objection to being classed as the metabolic brothers of the omnivorous pig may be gratified by our experience that no other mammal reacts less like man. On the other hand the typically carnivorous badger shows ketonuria, which in diabetes begins almost simultaneously with the glycosuria. The dog is the best and most human of animals in the laboratory as elsewhere. He talks with his eyes and tail instead of his tongue, and there are some metabolic differences of similar degree. But he has told us so much of what we know about diabetes that it would be important to find a way for him to reveal the one thing on which he has thus far given scanty and unsatisfactory information, namely, diabetic acidosis. There is evidence that the dog stands ready as usual to do his part, and the fault has been with us. Von Noorden and Mohr have tried to make the matter too simple by affirming [1] that if a dog is kept a long time on bread diet so as to accustom him to carbohydrate like man and then changed suddenly to strict meat diet, a heavy ketonuria results. No experiments are cited in support of this assertion, which would seem to be imaginary; at any rate it is untrue, as we have found in a sufficient number of dogs, some of which had lived on carbohydrate for their entire lives. But Neubauer states the observation that very young dogs may show ketonuria on fasting, thus presenting an unusually close similarity to man. Veterinary literature proves that dogs are susceptible not only to spontaneous diabetes but also to the termination in coma. Fasting phloridzinized dogs show heavy ketonuria, and von Mering, Lusk and others described the limp and semi-conscious state which may result. Marriott demonstrated ketonemia in such animals, and we have found high ketonuria and low carbon dioxide in the

[1] Von Noorden, Die Zuckerkrankheit, 1912, p. 137.

terminal condition, which therefore seems truly analogous to diabetic coma. But as usual there are differences between phloridzin poisoning and diabetes. According to Baer a phloridzinized dog shows ketonuria only when there is a negative nitrogen balance. Perhaps this is why Geelmuyden found fat to diminish the ketonuria. None of our experiments have dealt with nitrogen balance sheets, but the impression certainly is that phloridzinized dogs show ketonuria on diets moderate in protein and high in fat, and this is strongly in accord with the probabilities. The most important distinction lies in the effect of carbohydrate and protein. Benedict and Osterberg proved that protein feeding causes a fall of 50 to 90 per cent. in the ketonuria, even though the D : N ratios showed that all sugar formed from protein was quantitatively excreted. Obviously, protein does not work such a transformation in diabetic patients, and these authors correctly concluded that great caution must be used in interpreting the results of acidosis experiments in phloridzinized animals. The great majority of totally depancreatized dogs show only slight ketonuria and no coma or other acidosis symptoms. Sass, using the Loewy-Zuntz titration method, could detect no lowering of alkalinity in their blood. From the large number of depancreatized dogs in the Minkowski clinic, Allard was able to report several dying in coma with considerable ketonuria. Kirk notes some similar deaths in his pancreas-fed dogs, also a higher ketonuria when fat was fed along with pancreas. Apparently the lower D : N ratio of the depancreatized dog suffices to explain the less marked acidosis as compared with the fasting phloridzinized dog, especially in view of the large quantities of protein katabolized. The great objection to totally depancreatized and Sandmeyer dogs is their cachexia and defective digestion.

Having dogs with severe diabetes and satisfactory digestive power, and desiring to produce in them if possible a facsimile of clinical acidosis, it is reasonable to proceed by subjecting them to the same conditions as human patients. To the question whether successful results can thus be obtained in dogs, the experiments now permit answering yes; that acidosis can be regularly produced in dogs not merely in one way but in three ways, of which

gradations and combinations exist, but which are most conveniently described separately, in order to show the complete imitation of the human phenomena.

First we may take the classical treatment of severe diabetes. This has been based upon a too clever caloric conception. The tendency of the diabetic is to emaciate because of deficient assimilation. The superficially smart idea has been to force up his weight by the trick of crowding calories into the diet to replace those lost in the urine, and of supplying these calories in the form of a food of which the body has only slight ability to relieve itself by excretion, namely, fat. The dog is an ideal subject for such a treatment. On the one hand, by reason of his lower D : N ratio, he loses less sugar than the very severe human cases, and he has a natural high resistance to acidosis; on the other hand, he is able to digest and metabolize far more food per kilogram of body weight than any human being. Therefore, it is an interesting experiment to take a suitable dog, free from cachexia, and see what happens when he is forced either to hold or to gain weight in the presence of severe diabetes. He cannot long hold weight on carbohydrate or protein; the one food for the purpose is fat. It is like the old fancy of the irresistible force meeting the immovable body; and in the present instance either digestion or metabolism, no matter how strong, must break down. Sometimes it is the former. In some dogs, and in any dog if the diet is not carefully adjusted, vomiting, diarrhea, and loss of weight prevent a perfect result. The tendency to digestive disturbances is like that of human patients on similar treatment. If digestion and absorption remain adequate, the breaking down of metabolism is manifested by increasing acidosis. There is repugnance to fat and hunger for carbohydrate as in human patients, but the animal's wishes must be disregarded, as has been done in human cases, and the fat given forcibly if necessary. The highest fat diet is the most quickly toxic, but excessive quantities of fat are not required, and both protein and carbohydrate aid digestion and do not interfere with the result so long as fat is continued. In the long run suet is probably the form of fat best liked and digested. Talcum powder is useful in the diet to

control diarrhea. For the size of dogs used, the acidosis diet has sometimes been 150 to 200 grams suet and 200 to 400 grams beef-lung, or 100 to 150 grams suet, 200 grams lung, and 50 to 150 grams bread. Lipemia is present; there is malaise and depression of spirits as in patients with acidosis, and digestive upsets increase. If the animal is well suited for the purpose, if the diet is properly adjusted, and if there is enough day and night watching of all details, it can be shown that dogs thus go into fatal diabetic coma on full mixed diet. Dog 327 was our first and a very typical case. Table IV shows the clinical details of this final period.

Second, we may take the customary treatment of moderate diabetes and illustrate it in dogs. Suppose that suitable operation and overfeeding have produced a condition in which there is marked glycosuria on a kilogram of lung but sugar-freedom on 800 grams lung, along with a fair state of nutrition and entire absence of ketonuria. Now place the dog on 600 to 800 grams lung and 100 to 200 grams suet, according to the classical method. There is no glycosuria, weight is gained, and the condition is splendid for weeks and possibly months. The treatment is highly successful. Closer examination shows the presence of hyperglycemia and slight ketonuria, which are usual in the patients of corresponding type. Glycosuria follows, illustrating the "spontaneous downward progress" which the authorities describe. This is cleared up by a few fast-days on the Naunyn plan and the diet is again adjusted; it may now be 400 grams lung and 200 grams suet. The gain in weight continues as before, with hyperglycemia, ketonuria, and subsequent glycosuria. Again the fast-days are used and the protein diminished, so that the diet is perhaps 200 grams lung and 200 grams suet. The same cycle is repeated. Now the dog is in splendid condition and spirits, the coat sleek, the appearance such that he might create a good impression out walking in the park, only he has difficulty in remaining sugar-free on even the protein minimum, and the fat may be pushed higher to maintain nutrition against the repeated fast-days. If the dog has actually been kept fat, a fasting period about this time may diminish the glycosuria or it may remain

high. The previously lively and hungry animal begins to show a curious little mournfulness and complete repugnance to food. A day or two later vomiting of clear mucus begins, and the dog drinks and vomits water. The acetone reaction is heavy; the ferric chloride may be heavy or slight. The alkali reserve of the blood falls low, and the complete picture of patients who go into fatal acidosis on fasting is reproduced. Dogs of the type first described are also subject to this result of fasting if they have been kept fat enough, but fattening is easiest in absence of glycosuria. As in human patients, this form of acidosis more resembles the collapse or heart-failure type of Frerichs. The respiration is less typical and consciousness may be retained practically to the end. The outstanding features are the nausea and vomiting and the profound collapse of strength. Table II represents the terminal stage of this condition in dog 280.

Incidentally it may be noted that the cachexia which sometimes causes an apparent suppression of sugar formation in fasting depancreatized dogs is absent in these severely diabetic, partially depancreatized animals, so that their glycosuria and hyperglycemia typically persist almost or quite to the time of death.

The third type of acidosis in dogs is exemplified by diabetic animals kept free from glycosuria by regulated diet, or by those in which the amount of pancreatic tissue removed is not quite sufficient to give rise to diabetes. They are free from acidosis on protein diet or on fasting, but on a carbohydrate-free diet high in fat they sooner or later develop marked ketonuria. The protein ration may be governed by the capacity of the stomach. Probably high protein tends to increase susceptibility to diabetic glycosuria and diminish the tendency to ketonuria. These experiments also may extend over weeks or months, but we have proved upon many dogs that with enough fat in the diet the result is invariable. The qualitative acetone test is heavy but the quantitative output relatively small, generally below 1 gram. An example of this condition is given incidentally in the record of dog 356 (Table V), with potentially severe diabetes. Partially depancreatized non-diabetic dogs on a diet of 150 to 300 grams suet

TABLE IV.—DOG 327 (PARTIALLY DEPANCREATIZED).

Date. 1916.	Blood.					Urine.							Weight,† kg.	Diet.	Remarks.
	Plasma sugar, %	Hb. %	CO_2, capacity. Vol %	Acetone, qual.	Lipemia, qual	Volume, c.c	Acetone, qual.	Total acetone,* mgm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.	Sugar, gm.			
April 15–16	..	..	..	..	..	922	++++++	91.3	9.082	1.259	7.22	57.33	..	200 gm. lung 200 gm. suet 50 gm. bread	Vomiting and diarrhea frequent during this period.
16–17	0.370	106	22.1	+	++++++	406	++++++	144.8	3.059	0.875	3.50	15.63	..	"	
17–18	0.400	108	29.0	++	++++++	530	+++++	129.9	6.201	0.737	8.40	30.81	19.0	"	
18–19	..	..	..	..	..	1186	+++++	134.0	10.081	1.257	8.00	66.22	18.4	"	Rapidly increasing acidosis symptoms.
19–20	0.400	..	18.5	+++	+++++++	1350	..	489.2	11.475	1.633	7.05	56.70	18.2	"	
20–21	0.314	..	23.3	..	+++++++	1480	..	389.2	10.952	1.717	6.36	51.80	..	"	
21–22	0.500	..	21.4	+++	+++++++	811	..	210.7	4.542	..	..	17.84	16.0	...	Coma.

* Total acetone bodies as acetone.

† Note precipitous fall.

TABLE V.—DOG 156 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.						Urine.‡								Weight in kg.	Diet.
	Plasma sugar, %	Hb., %	CO_2 capacity. Vol %	Acetone, qual.	Total acetone,* mgm. per 100 c.c.	Lipemia, qual.	Volume, c.c.	Reaction.	Acetone, qual.	Total acetone * mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N, ratio.		
Aug.																
24–25	0.200	..	..	..	..	..	269	..	+	..	2.60	7.500	0.820	9.15	11.1	400 gm. suet.
25–26	0.124	106	..	..	..	..	160	..	0	..	+	4.110	0.510	8.07	..	300 gm. suet.
26–27	0.111	..	..	..	..	..	246	..	0	..	0	2.100	1.560	1.35	..	200 gm. suet.
27–28	0.099	..	53.8	..	..	..	192	..	0	..	0	2.670	1.130	2.36	11.4	100 gm. lung; 200 gm. suet.
28–29	..	..	..	..	..	..	352	..	0	..	0	4.100	1.640	2.50	..	Fasting.
29–30	..	..	..	..	..	..	382	..	0	113.1	0	3.570	2.100	1.70	..	100 gm. lung; 100 gm. suet.
30–31	..	..	..	..	..	..	172	..	+	..	0	2.510	1.360	1.84	..	100 gm. lung; 200 gm. suet.
31– 1	..	..	..	..	..	..	140	..	0	..	0	1.580	0.782	2.02	11.4	150 gm. lung; 150 gm. suet.
Sept.																
1– 2	..	..	..	..	..	..	176	..	+	..	0	2.410	0.950	2.54	..	150 gm. lung; 250 gm. suet.
2– 3	..	..	..	..	..	..	160	..	0	..	0	4.320	1.320	3.28	..	150 gm. lung; 250 gm. suet.
3– 4	..	..	..	..	..	..	116	..	+	..	0	1.540	1.020	1.51	..	150 gm. suet.
4– 5	..	..	..	..	..	..	295	..	+	64.9	0	1.593	1.180	1.32	11.75	100 gm. lung; 200 gm. suet.
5– 6	..	..	..	..	..	..	140†	..	++	22.4	0	0.975	0.364	2.66	..	
6– 7	0.095	90	48.5	0	..	0	357	..	+	86.0	0	3.642	1.175	3.08	11.80	Ditto.
7– 8	..	..	..	..	..	..	258	..	+	49.0	0	2.296	0.413	5.55	..	Ditto.
8– 9	0.083	..	57.9	0	..	0	260	..	+	44.2	0	..	1.000	..	..	Ditto; 8 gm. sod. bicarb.
9–10	..	..	..	..	..	..	842	Alkaline	..	101.0	0	6.399	1.263	5.07	..	Ditto; 5 gm. sod. bicarb.
10–11	0.093	86	67.3	0	..	0	378	Alkaline	0	49.1	0	5.640	0.491	11.50	11.81	Ditto; 10 gm. sod. bicarb.
11–12	..	..	..	..	..	..	380	Alkaline	0	38.0	0	1.642	0.144	11.40	..	Ditto.
12–13	..	..	..	..	..	..	904	Neutral	..	99.5	0	0.814	0.181	4.50	..	Ditto; vomited.
13–14	..	..	..	..	..	..	342	Alkaline	+	68.5	0	2.743	1.180	2.32	..	Ditto.
14–15	0.115	105	67.2	?	..	++++++	170	Alkaline	++++	64.8	0	1.578	0.876	1.80	..	Ditto.
15–16	0.121	93	60.5	+	..	++++	360	Alkaline	++++	84.0	0	3.384	1.332	2.56	..	Ditto.
16–17	0.123	..	58.6	..	..	+	438	Alkaline	++++	53.6	0	3.503	1.051	3.34	..	Ditto.
17–18	0.121	96	64.3	0	..	+	412	Acid	..	30.8	0	0.676	0.144	4.68	12.05	Ditto.
18–19	0.128	..	51.9	0	..	+	220	Alkaline	++++	41.8	0	1.786	0.759	2.36	..	Ditto.
19–20	..	..	..	..	..	..	418	Alkaline	++++	79.7	0	5.643	1.672	3.37	..	Ditto.
20–21	0.149	105	..	+	25.5	+++	664	Alkaline	++++	117.4	0	2.523	1.195	2.10	..	Ditto.
21–22	..	..	..	..	..	..	768	Alkaline	+++++	93.7	0	2.611	1.459	1.79	..	Ditto; vomited.
22–23	..	..	..	..	..	..	670	Acid	..	34.4	0	1.983	0.670	2.95	..	Ditto.
23–24	..	..	..	..	..	..	344	Neutral	..	60.0	0	1.238	0.241	5.12	..	Ditto.
24–25	..	..	..	..	..	..	600	Alkaline	++	..	0	3.108	1.440	2.16	..	Ditto.
25–26	0.179	108	59.5	+++	30.5	++++	870	Acid	++++	..	0	2.302	1.657	1.40	12.20	Ditto.
26–27	..	..	..	..	..	..	790	Alkaline	..	213.3	0	2.465	1.422	1.74	..	Ditto.
27–28	..	98	63.3	0	18.9	+	733	Alkaline	..	43.9	0	1.833	1.393	1.32	..	Ditto.
28–29	0.322	86	61.4	+	..	0	400	Alkaline	..	20.8	0	2.080	0.780	2.66	..	200 gm. lung.
29–30	0.400	..	..	0	31.2	0	565	Alkaline	..	26.2	0	5.763	1.441	4.00	..	
30– 1	0.435	89	..	..	35.7	..	550	Alkaline	+	25.3	5.65	4.554	1.953	2.33	..	
Oct.																
1– 2	0.250	92	61.4	0	23.2	0	468	Alkaline	+	..	0	2.621	0.772	3.40	..	
2– 3	0.192	95	59.5	0	..	0	636	Alkaline	0	..	0	2.582	0.670	3.85	..	
3– 4	0.175	88	59.5	0	..	0	605	Alkaline	0	..	0	2.009	0.484	4.14	..	Fasting.
4– 5	0.208	82	59.5	0	..	0	828	Alkaline	0	..	0	2.385	0.621	3.84	..	
5– 6	0.235	88	63.3	+	..	0	842	Acid	0	..	0	2.055	0.505	4.07	..	
6– 7	0.169	76	..	0	..	0	870	.	0	..	0	2.242	0.686	3.25	..	
7– 8	..	..	..	..	..	..	600	Alkaline	0	..	0	..	0.420	..	..	
Nov.																
3– 4	0.200	..	..	..	..	..	..	..	..	..	..	..	..	..	8.15	200 gm. lung.

‡ Not catheterized. * Total acetone bodies as acetone. † Incomplete specimen.

and perhaps an equal amount of lung may thrive in spite of ketonuria for a longer or shorter time. Ketonuria is apt to be slight. But the final outcome appears in one of two forms. One may be digestive failure and consequent loss of weight and strength, with cessation of ketonuria. In the other form the routine measures against vomiting and diarrhea may succeed, but the end comes with a remarkable spastic and ataxic condition, with terminal weakness, convulsions and death. The absence of ketonuria in adult normal dogs on fasting has been confirmed, and has been found true also on high fat diet extending over several months and still continuing. Tests on puppies are only beginning. One young collie suddenly showed a heavy acetone reaction after two weeks of fasting. High fat diet was immediately given. On the third day of this the dog, which was not known to have been pregnant, aborted. This was some two weeks ago. The acetone reaction with low quantitative values has not ceased, but the dog continues to act well. It is not known whether this idiosyncrasy is present because the dog is young, or because of the collie breed, or because of the pregnancy. Normal controls flourish indefinitely, without ketonuria or with only traces, on the same fat-protein diet which causes acidosis in partially depancreatized dogs. A certain number of normal dogs with a sufficient preponderance of fat over protein in the diet develop ataxia and fatal intoxication seemingly identical with that of partially depancreatized dogs, but ketonuria is generally absent or slight. Digestion is upset in them as in the partially depancreatized animals; accordingly, ketonuria cannot be attributed to fatty indigestion. This state of intoxication will require subsequent mention. In partially depancreatized animals the sugar tolerance is diminished. If the ketonuria be interpreted as a diminished fat tolerance, it affords no evidence concerning the unity or plurality of the pancreatic secretion, and in absence of evidence the presumption remains in favor of the former. These experiments are mainly useful as showing that a species which normally has a high resistance to acidosis is made readily susceptible by partial pancreatectomy, and as thus furnishing conclusive proof that the simple balance between fats and other

foods does not alone govern ketogenesis, but that a specific internal function of the pancreas is at least one of the factors concerned.

Of various points perhaps deserving mention, six features of canine acidosis will be chosen for separate consideration. First, there are some peculiarities of species seen in the clinical picture. A characteristic of human coma is that the cerebral centers are anesthetized while the respiratory center is stimulated. It may be taken as a general rule that dogs lose consciousness less readily than men, and this applies to their diabetic coma. They begin by showing weakness, drunken gait, and dyspnea especially on slight exertion. The symptoms increase until the animal cannot stand, and the Kussmaul breathing may be typical. The corneal reflex is practically never lost, and even attention to surroundings may be preserved almost to the last. It might appear that the motor centers are selectively intoxicated, until observation shows there is apparent absence of pain in the exposure of bloodvessels or other operations, so that the sensory depression is fully equal to that in human coma, in which a knife-cut frequently provokes some response. The low blood-pressure emphasized by Ehrmann and the soft eyeball noted by Riesman and others have not been tested. Diarrhea sometimes occurs with human coma; in dogs it is invariably present and tinged wtih dark blood. It occurs whether the coma is produced by feeding or fasting, by diabetes or by phloridzin. It is therefore of metabolic, not of digestive origin. At autopsy the liver is typically large and fatty, and much fat may be present in the body. There is more or less venous engorgement of the intestine and other viscera, which is the only apparent explanation of the bloody diarrhea, though the bowel contents begin to appear bloody only toward the rectum.

Second, there is the obvious question of the influence of reaction. Toward the end the carbon dioxide capacity of the plasma falls as in human cases, and to a quite similar level. But one advantage of studying the same phenomenon in various species is seen in the fact that in the dog it is easy to maintain normal or supernormal alkalinity of the blood from start to finish, or to raise it suddenly toward the end when it has fallen. In man this is difficult to accomplish even by the highest alkali dosage,

but some clinicians have asserted that continuous alkalinity of the urine has failed to save their patients. A few personal observations, and my conception of the acidosis process, have convinced me that this view is essentially correct. Probably the typical dyspnea and coma never occur in man or dog except with acid intoxication. Probably the upholders of the acid intoxication theory of coma are correct on this point, which is, after all, their main contention. Where they seem to be clearly wrong is in the more important matter of extending this idea to mean that a maintenance of reaction would prevent intoxication. Conceivably the secret of the improvement sometimes produced by bicarbonate may lie in an unloading of toxic substances from the cells rather than in a shifting of the alkali-acid equilibrium *per se*. Aside from a possible, very brief, rise in blood-pressure, sodium bicarbonate intravenously or otherwise brings no visible benefit to a dog dying of acidosis. Keeping the alkaline reserve of the plasma continuously normal by means of it or any form or combination of alkali salts apparently does not prolong the life of a diabetic dog by a single day. The experiments support the conception that acidosis and coma essentially represent an intoxication due to a specific breakdown in metabolism, and that the tendency to alteration of reaction is only an incidental phenomenon.

A third point, closely connected with this, is the ammonia excretion. This was considered the most reliable index of acidosis until the introduction of the tests of alveolar air and blood. Researches beginning with Walter have established that different species vary in their ability to protect themselves against acid intoxication by ammonia formation, and that the quantity of ammonia that can be produced is partly governed by the amount of protein in the diet. Owing particularly to the work of Magnus-Levy and his masterly reviews of the literature, the prevalent tendency is to see in the ammonia solely a reaction to acid poisoning. Therefore, it is well to read the excellent review by Ewing, which gives fairer consideration to other factors possibly concerned. Since the early work of Minkowski, Schütz and others, it has seemed that the liver function is one governing factor, and

Allard, Rolly and others have upheld the importance of this element in diabetic acidosis. The dog experiments promise to contribute information on this point, but they do not yet permit a conclusion. Normal dogs seem regularly to show low ammonia notwithstanding high fat diet. One of our supposedly normal dogs injured its back while out for exercise, with resultant transitory paraplegia and subsequent polyuria. This dog thrives on either carbohydrate or fat, but shows low ammonia on the former and high ammonia on the latter. Partially depancreatized dogs react to fat diet with such a vigorous ammonia production that the urine is sometimes turned alkaline. Dog 356 (Table V) here gives one example. Alkaline urine on protein-fat diet makes any experienced investigator think of cystitis. To exclude this we now for the most part omit all catheterization and test the animals with a change of food or with alkali. When carbohydrate diet or, as with dog 356, sodium bicarbonate causes a prompt fall in the ammonia and rise in the $N:NH_3$ ratio, cystitis is considered improbable. It is not certain that alkali must necessarily reduce ammonia excretion to normal. The ammonia relations shown in dog 356 and others would seem indicative of reaction or over-reaction to acid. Over against these are the relatively low ammonia figures and high ratios in dog 327 (Table IV), notwithstanding the falling alkalinity of the blood and impending death in coma. The essential known difference between the animals is that dog 327 constantly had carbohydrate in the diet. It is possible that the exceptional results are accidental, and as yet we lack the necessary series of experiments to say that they are significant.

The acetone bodies represent a fourth point requiring brief notice. In general, dogs excrete less of them per kilogram of body weight than human patients. It must be remembered that the excretion by human patients is generally not very high except under the influence of alkali therapy, and coma is possible with low ketonuria. The ketonemia seems to be on a par with that of human patients. It is as if the dog's kidney were relatively impermeable to acetone bodies. Also, sodium bicarbonate seems inefficient to sweep them out. A further distinction is that

acetone represents a higher proportion of the total acetone bodies than in severe human cases. There is greater similarity to the milder human cases in this regard. What significance it may have in connection with the natural difference between dog and man respecting acidosis is unknown. Miss Wishart conceived the idea of applying the Rothera acetone test to the blood plasma. The test has proved very useful as a routine in the animal work. It has also given dependable results when applied to human patients here and in Dr. Joslin's clinic in Boston. The significant color range varies from the faintest tinge up to the deepest permanganate color. The proteins or other substances in plasma seem to cause no interference. The reaction appears unsuited for exact quantitative application, but it gives a quick, rough idea whether there is dangerous ketonemia or not and whether a quantitative determination is worth while; and as its results do not always run parallel to the urinary reactions, it would seem that qualitative tests are more valuable in the plasma than in the urine. Preformed acetone is actually trivial in amount, and the substance in blood and urine indicated by the nitroprusside test and commonly referred to as acetone is essentially aceto-acetic acid (Arnold; Embden and Schliep; Folin and Denis; Hurtley; Kennaway). Specific poisoning with acetone bodies has been the principal hypothesis opposed to the acid intoxication theory of acidosis. In denying the latter view we are not necessarily thrown back upon the former. The cause of damage from the metabolic breakdown may or may not be subject to chemical analysis by present known methods. The present work adds to the means for approaching the problem. It is possible that the acetone bodies may some day prove to be an index rather than the cause of the intoxication in acidosis.

A fifth point for mention is the behavior of the kidney, which has recently been studied in human diabetics by McLean and more particularly by Fitz, but which time has not permitted investigating in our animals. Incidental observations show that the usual polyuria of severely diabetic animals is generally diminished on high fat diet, and oliguria is frequent in spite of high sugar percentages in blood and urine. For some reason thirst is lacking,

so the change is not altogether renal. The kidneys are sometimes remarkably impermeable to sugar, after sugar feeding in mild cases but more notably after fat feeding in severe cases, when it is possible to have 0.4 per cent. blood-sugar without glycosuria. An example is furnished by the record of dog 356 (Table V). Neither water nor sodium bicarbonate has been observed to cause edema, but the latter seems not to produce such thirst and diuresis in acidosis animals as in normal ones, and perhaps this is why acetone bodies are not swept out as in the human. Albuminuria is common in acidosis and in simple fat intoxication, but the few observations made have not shown casts. The kidneys of dogs with advanced acidosis have always shown gross and microscopic alterations as far as yet examined, the Armanni vacuolation of certain tubule cells being the most constant. Glycogenic degeneration described by Ehrlich has not always been demonstrable by Best's carmine stain. From the absence of edema after nephrectomy and other known facts, it is doubtful if dogs are suited for accurate imitation of the renal peculiarities of human diabetics, but it seems probable that excessive fat ingestion has directly or indirectly an injurious effect on the kidneys in both patients and dogs, and that this feature is worthy of more study than we have been able to give it.

The sixth and last point for special mention is the general position of fat in the dietary. The early investigations of the total metabolism founded the conception of the caloric requirement and isodynamic equivalents. A protein minimum has been partially worked out. It has been proved that carbohydrate has a slightly greater sparing action than fat, and particularly by Mendel has been established the importance of individual amino acids for nutrition and growth. The need of salts is known, and the so-called vitamines are a recent discovery. This practically sums up the existing knowledge of nutrition. Against the prevalent belief that a starving organism is benefited by whatever food it can obtain, should be raised the question whether this is ever true of any non-protein food taken in quantities approaching the total caloric requirement each day. The question pertains to the benign carbohydrate. Concerning fat there is no question. Fat

unbalanced by adequate quantities of other foods is a poison. It should be recalled that carnivorous animals subsist largely on protein, and though the Eskimo consumes much fat, he also, according to the Krogh report, eats several kilograms of lean meat daily. After a few days of pure fat diet the most voracious cur will starve to death before he will touch it further, and the more strictly carnivorous cat is still less tolerant of fat-rich diet. Against forced feeding the organism protects itself by vomiting, diarrhea, and remarkable cessation of absorption. No form of emulsification or admixture with talcum or other inert substances to give consistency resembling that of the normal ration avails against this toxic action. The small proportion of protein contained in cream or suet gives only partial protection. The same result follows more slowly whenever the proportion of fat to protein or carbohydrate in the diet is too high. The craving of diabetic patients for carbohydrate is often illustrated in such dogs. It should be worth while to determine a law of balance for normal animals. Not only has the diabetic animal a specific sensitiveness to fat, but on low protein ration it must be unable to bear as much fat as an animal on high protein. If the danger of glycosuria prevents increasing the protein, intoxication can be avoided by diminishing the fat. The animal is thinner but safer, hungry instead of nauseated. Diabetic patients have been treated on protein requirement and caloric computations and on general experience of what they will endure. One feature of this experience is that the great majority of severely diabetic patients acquire a repugnance to the prescribed diet and refuse to endure it. By will-power they sometimes endure it for a time. Raulston and Woodyatt's patient adhered for nearly three weeks to a diet of three eggs and 800 c.c. of 16 per cent. cream daily. They employed this as a temporary measure, but such low protein, full calory diets have been the ideal of the best workers under the Naunyn method. The fact is that such a diet will send a diabetic dog into coma, and it is questionable how long normal dogs could tolerate it. It thus appears that patients were right in much of their conduct, and their stealing of carbohydrate was not entirely due to original sin but was rather prompted by physiological

necessity. They live in fair comfort on moderate protein and little or no carbohydrate as long as the fat is kept suitably low. They behave much more rationally toward simple hunger for all classes of foods than they did toward the former excessive craving for carbohydrate. Lack of self-control still claims many victims, but the proportion of patients willing to follow diet faithfully has been increased by reason of the more natural balance of foods in the diet.

III. INFLUENCE ON CARBOHYDRATE UTILIZATION

The third phase of the rôle of fat in diabetes to be considered now is its influence on carbohydrate utilization, on hyperglycemia and glycosuria.

The literature on this subject is scanty. A small number of writers believe it probable that sugar is formed from fat. A somewhat greater number, including Magnus-Levy, admit the possibility. The great majority recognize the occurrence of such a process in plants, but find no evidence of it in animals. Attempts have been made to demonstrate it in animal experiments, but these have failed so completely that they are not worth reviewing; whereas, on the other hand, the non-increase of sugar after fat feeding, the dextrose-nitrogen ratio, and the respiratory quotient, as found by Lusk and others, offer seemingly conclusive proof of the absence of such a transformation in the intense sugar-hunger of phloridzin-poisoning. Although Donkin insisted on skim milk for his milk cure, and that cream spoiled it, the first to assert that fat increases diabetic glycosuria was Lichtheim, whose perfectly correct statement is mentioned with disapproval by Weintraud. Weintraud argued that even if fat should in certain cases cause the excretion of a few grams of extra sugar, the food value of the fat is far greater than this, so there is clear benefit. This has remained the position of the Naunyn school. Lenné, von Noorden and others, who hold extreme views of conversion of fat into sugar, nevertheless use fat to make up a full caloric ration. Von Noorden confesses to prescribing fat perhaps more liberally than anybody else. He and Falta and other pupils mention occasional so-called "fat-sensitive" patients whose glyco-

suria is increased by fat feeding; but this effect is said to follow only the overnutrition produced by excessive fat ingestion, and fat in the quantities practically employed is held not to increase glycosuria, because if it were withheld its place in metabolism would supposedly be filled by body-fat. I have reviewed elsewhere reports of dextrose-nitrogen ratios supposedly proving sugar formation from fat in diabetic patients, but actually proving they were not adequately watched; also the other observations from Griesinger down to Benedict and Joslin and Du Bois demonstrating that no higher dextrose-nitrogen ratios than Lusk's 3.65 value are found in even the severest clinical diabetes; and the respiratory quotients further assure the non-formation of sugar from fat. In view of the general acceptance of these facts, it is natural that the possibility of increase of glycosuria from fat feeding should be generally ignored. If an occasional voice asserts from time to time that fat increases glycosuria, the protest is directed only against fat rations considered excessive, and only the most slight and transitory undernutrition has been countenanced by such authors.

It is likewise natural that the glycosuria attributed to fat should be small, and that the so-called sensitiveness should be apparent in relatively few cases. The effect of fat was above characterized as insidious and cumulative, even with respect to the acetone bodies which are formed from fat; and at least an equally occult influence should be anticipated with respect to sugar, which seemingly is not formed directly from the fat itself. Its action, though not absent in mild cases, is necessarily difficult to demonstrate. The heavy and variable glycosuria of average severe cases and the already maximal output in the extreme cases, hopelessly mask the effect of fat, which therefore is only demonstrable rather doubtfully in an intermediate group. Once more the severe cases freed from glycosuria and acidosis afford the best clinical experimental material. Dr. Fitz has been performing some experiments of this type, with unusually complete laboratory observations. One of his protocols is here reproduced (Table VII). The patient, who developed diabetes at the age of fifteen, is now nineteen, and has been under treatment at the Institute

TABLE VI.—DOG 394 (PARTIALLY DEPANCREATIZED).

Date, 1916.	Blood.‡					Urine.§							Weight, kg.	Diet.	Remarks.
	Plasma sugar, %	Hb., %	CO_2, capacity, Vol %	Total acetone,* mgm. per 100 c.c.	Total fat, plasma, %	Volume, c.c.	Total acetone,* mgm.	Sugar, gm.	Total nitrogen, gm.	Ammonia nitrogen, gm.	N : NH_3-N ratio.	D : N ratio.			
Aug.															
6–7	..	..	..	..	..	1731	360.0	48.5	..	..	..	..	..		
7–8	0.285	82	47.1	83.2	..	1302	248.0	43.4	..	..	..	..	..	100 gm. lung; 100 gm. suet; 100 gm. bread	
8–9	0.270	..	51.0	94.5	0.566	1178	..	60.8	5.30	..	..	..	10.1		
9–10	0.250	106	51.0	36.4	..	1900	416.0	80.0	7.40	..	..	..	..		
10–11	0.232	92	..	18.5	0.566	800	130.5	52.0	4.71	0.44	10.71	..	..		
11–12	0.204	..	..	44.8	0.583	630	134.9	23.3	9.50	0.85	11.18	2.45	..		
12–13	..	..	..	..	..	3080†	591.0	19.1	8.65	1.23	7.04	2.21	..	400 gm. lung; 100 gm. suet.	
13–14	0.286	103	32.8	50.1	..	1605	596.0	32.1	11.40	1.61	7.08	2.82	..		
14–15	0.364	95	40.4	23.4	0.490	704	182.4	22.8	9.10	0.91	10.00	2.50	10.0		
15–16	0.250	95	31.9	80.4	0.290	646	124.8	19.4	8.30	0.84	9.88	2.34	..		
16–17	0.377	95	31.9	..	2.380	1030	224.9	35.2	9.27	1.40	6.63	..	9.77		
17–18	0.322	..	51.9	41.0	..	1800	195.1	72.0	10.80	1.62	6.68	..	9.70	400 gm. lung; 100 gm. suet; 100 gm. bread	
18–19	0.365	90	38.5	30.6	1.840	820	288.0	41.0	9.50	0.82	11.58	..	9.80		Dark diarrhœa.
19–20	..	..	..	..	..	2350†	742.1	47.0	10.10	1.22	8.30	..	..		
20–21	0.276	..	30.9	73.2	0.430	662	119.6	49.2	8.15	0.76	10.72	..	9.76		
21–22	0.263	51	..	41.1	0.765	406	116.7	13.2	..	0.67	..	..	9.50		
22–23	0.295	35	32.8	39.8	0.591	515	226.5	19.5	7.70	0.77	10.00	2.53	9.50		Unwell; entire diet forced.
23–24	..	..	..	..	..	584	163.8	10.7	5.95	0.73	8.15	1.80	9.07		Eats all diet promptly.
24–25	0.214	39	34.7	36.9	0.825	820	316.8	28.7	8.60	0.90	9.55	3.34	9.30	400 gm. lung; 200 gm. suet.	Seriously ill; fed forcibly.
25–26	0.314	26	40.9	29.2	1.090	686	332.2	15.6	6.65	0.82	8.12	2.35	9.16		
26–27	0.237	..	48.1	..	..	680	214.5	14.3	9.85	0.88	11.15	1.45	..		5 gm. sodium bicarbonate.
27–28	0.256	25	60.5	60.3	0.785	390	170.0	7.2	6.00	1.88△	3.19	1.20	8.75		
28–29	0.354	22	54.8	26.2	0.895	675	230.9	14.1	6.75	1.59△	4.25	2.09	8.51	Not fed	Good condition and spirits.

‡ Blood drawn twenty-four hours after feeding. § Catheterised to separate diet periods. * Total acetone bodies as acetone. † Water spilled. △ Cystitis?

TABLE VII.—PATIENT B. D. P.†

Date. 1916.	Blood.					Urine.							Weight, kg.	Diet.▲			
	Urea nitrogen, mgm. per 100 c.c.	Plasma acetone,* mgm. per 100 c.c.	Plasma chloride, %	Sugar, %	Plasma, CO_2 capacity. Vol %	Volume, c.c.	Total nitrogen, gm.‡	Ammonia nitrogen, gm.	N : NH_3-N ratio.	Acetone,* gm.	Chloride, gm.	Sugar, gm.		Protein, gm.	Fat, gm.	Calories.	NaCl, gm.
Sept. 29–30	..	25	0.594	0.204	63.0	4150	4.31	0.54	7.98	1.67	12.85	Trace	37.8	7.4	13.5	150	10
30– 1	..	..	..	..	..	3235	7.14	0.94	7.60	2.56	6.95	Neg.	36.4	33.0	34.0	450	10
Oct. 1– 2	..	..	..	..	..	3380	8.00	0.98	8.16	2.72	3.89	"	36.1	40.0	47.0	605	10
2– 3	..	33	0.606	0.172	65.4	3560	8.00	1.00	8.00	2.43	8.20	"	36.1	40.0	52.0	650	10
3– 4	..	..	..	..	..	3765	9.08	0.94	9.65	1.85	10.00	"	36.1	40.0	57.5	700	10
4– 5	6.9	25	0.593	0.143	66.3	3970	8.65	0.95	9.10	2.01	13.30	"	36.1	40.0	63.5	750	10
5– 6	..	..	..	..	..	3995	7.75	1.00	7.75	2.62	11.80	"	36.0	40.0	68.5	800	10
6– 7	..	24	0.588	0.192	67.4	3360	8.30	1.44	5.76	..	11.30	..	35.6	40.0	73.5	850	10
7– 8	..	..	..	..	..	3595	9.67	0.93	10.40	2.24	7.74	"	35.9	40.0	80.0	900	10
8– 9	..	..	..	..	..	3745	10.70	1.05	10.20	1.63	11.60	"	35.8	40.0	85.1	955	10
9–10	7.0	26	..	0.204	63.0	3555	9.70	0.89	10.90	1.48	11.90	"	35.9	40.0	90.0	1000	10
10–11	..	..	..	..	..	3835	10.25	0.84	12.20	0.96	12.45	"	35.8	40.0	95.0	1050	10
11–12	..	24	0.582	0.182	68.8	3530	8.26	0.84	9.85	1.35	11.12	"	35.5	40.0	100.0	1100	10
12–13	..	..	..	..	..	3290	9.71	0.95	10.21	1.64	9.37	Traces	35.6	40.0	105.0	1150	10
13–14	..	25	0.581	0.200	65.9	3270	7.64	1.18	6.50	2.50	8.82	"	35.5	40.0	110.0	1200	10
14–15	..	..	..	..	..	3465	10.60	1.18	9.00	3.46	10.39	"	35.6	40.0	115.0	1250	10
15–16	..	28	0.588	0.176	61.2	3120	12.25	1.34	9.15	4.40	8.26	1.85	35.4	40.0	120.0	1300	10
16–17	9.9	..	..	..	..	3140	12.20	1.48	8.25	2.86	10.98	21.32	35.6	40.0	120.0	1300	10
17–18	..	..	..	..	..	3330	10.20	1.63	6.25	4.16	8.66	13.32	35.7	40.0	120.0	1300	10
18	8.4	30	0.587	0.221	59.8	..	..	..	..	..	..	..	..	..	Fasting		

† Entire experiment by Dr. Fits. * Total acetone bodies as acetone. ‡ Note increased nitrogen output as fat is increased.

▲ 300 gm. thrice-boiled vegetables daily not reckoned; also 300 c.c. soup daily, containing 1.5 gm. N., not included in the protein figures.

for two years. She represents one of the cases in which tolerance is built up very slowly and with difficulty, and on account of tenement environment she loses in a few weeks at home as much as is gained in months at the hospital. Her general condition and power of assimilation are therefore known by long experience. The record begins with high blood-sugar produced by a slightly excessive previous diet. The diet throughout contained a fixed quantity of thrice-boiled vegetables, but no other possible source of carbohydrate. The procedure consisted in keeping the protein intake constant and increasing the fat by about 5 grams daily. The peculiarities concerning chlorides and other features will be discussed by Dr. Fitz elsewhere. The ketone and ammonia excretion increased moderately. The blood sugar first fell, then rose, as the fat was increased. The patient felt better on the higher fat. Such well-being is transitory. Glycosuria appeared in traces and increased to 21 grams. High glycosuria and acidosis can be produced by continuing such an experiment, but safety required checking the injury here by a fast-day. It is feasible in selected cases to show that the symptoms subside on simple omission or reduction of fat. This patient is an example of those who can demonstrably live in fair comfort and nutrition for at least several years on low diet almost or absolutely free from carbohydrate, but who would die rather promptly if the traditional building-up process with fat were attempted.

The earliest experiments showing the benefits of continued reduced nutritional level in diabetes were performed on dogs. Notwithstanding the evident clinical results in severe cases, there remain physicians who, conceding that such methods may be useful for such cases, find in their experience that patients feel best on liberal nutrition, and see no harm in allowing plenty of fat in the cases in which no immediate injury is perceptible. Also, there are other clinicians who hold that alleged radical differences between diabetic patients prevent drawing general conclusions or treating according to a unified broad conception, and who emphasize spontaneous fluctuations due to infections or other causes, and who try to draw distinctions between the properties of various kinds of fats, and who maintain the comfortable inter-

pretation that bad results under their methods are due to a progressive downward tendency inherent in the condition itself. By choosing the severest cases obtainable and including the poor and ignorant we have made a high death-rate inevitable. Furthermore, our own management has not been perfect, and we have sometimes given too high diets and committed other mistakes. This record might be pointed to in support of the allegation that while fasting is good for coma, and has in fact been employed by others previously, the end result is the same anyhow, and in deciding between coma and starvation it is better to choose the former and keep the patients as comfortable as possible. In defense we might point to the very high proportion of these patients apparently saved and improving and enjoying even comfort and usefulness in cases and to an extent apparently impossible under any former methods. Certainly the experience of the great majority of specialists and general practitioners has declared favorably for the benefits of the new plan, and it would not be possible for a treatment to receive a more cordial reception by the medical profession. But both the permanent establishment of the practical treatment on a basis not shaken by every wind of doctrine, and the full determination of the theoretical and scientific significance of the changes thus produced in the diabetic condition, require a clear demonstration of the principles at issue in animal experiments, in which all extraneous and accidental factors can be excluded, and facts concerning the rôle of fat in relation to diabetic glycosuria and carbohydrate metabolism can be proved by methods beyond the scope of the personal equation.

The first step in such an investigation is to define the potentialities of the experimental material. The material consists of dogs or other animals with injury of assimilation produced by a surgical resection. They are seemingly free from variations due to heredity or the innate tendencies ascribed to human patients. Their special peculiarities and possibilities must be learned. Glycosuria is more liable to cease spontaneously in cats than in dogs, apparently owing to a slower tendency to degeneration and a greater power of recovery in their exhausted islets. Thiroloix

and Jacob first announced that mildly diabetic dogs may be sent into the severe fatal form by carbohydrate overfeeding, like human patients, but they gave no description of controls, and their observations were apparently not long enough to reveal the final fate of the dogs not fed on carbohydrate. On first coming to the Rockefeller Institute over three years ago, I set apart some of the first dogs for prolonged experiments covering this point. Some were to be subjected to successive removal of small pancreatic fragments for microscopic and other purposes. Others after one initial operation were merely kept on certain diets. Shorter tests under a year in length were performed on other dogs and other species. No animals succumbed to operation, but a number to the environment. The finished series is not as perfect as planned, but is adequate for decisive results. The proportion of the pancreas which must be removed to produce a given grade of diabetes is fairly constant in a given species, though the rare individual exceptions are sometimes marked. There are great differences between species, which are independent of the natural sugar tolerance, diet, pancreatic structure, or any other known factors. The general tendency of the pancreas is to hypertrophy after partial ablation, most markedly in young animals, as Homans stated. Extirpation to any point short of producing diabetes causes no tendency to degeneration of the remnant or to downward progress clinically. When the operation is sufficient for mild diabetes, the food tolerance as ascertained after allowing a few weeks for recovery from trauma will generally hold good for a number of months on suitable diet. There is a tendency to some gain in tolerance, but this is usually easy to break down. It is hard to distinguish the true from a false gain in tolerance, characterized by hyperglycemia without glycosuria. Previous authors have reported this phenomenon after repetitions of adrenalin and in old human diabetes. It is present at a certain stage of overfeeding with sugar, protein, or fat. Part of it may represent renal damage, but a part is probably some reaction connected with the basic nature of diabetes. Within proper limits the animals are very valuable for testing

the effects of all sorts of agencies upon the carbohydrate and other assimilation and for distinguishing between diabetes and accidental glycosuria. The downward progress conclusively shown by feeding beyond the tolerance with carbohydrate or protein has been previously outlined. The experiments of feeding within the apparent tolerance have been only recently coming to completion. Dogs with a limited carbohydrate tolerance, when kept long enough at normal weight with carbohydrate below the limit, or on lean meat only, or on mixed lean and fat, finally show a gradual fall in tolerance, and all but one of the animals of this series have died of diabetes. The remaining one, now on a protein-fat ration, not only has lost all carbohydrate tolerance but shows active diabetes in the form of constant hyperglycemia and ketonuria. There is no reason why diabetes in an Eskimo should not begin in this way, but the ordinary human diet is such that glycosuria precedes ketonuria. The sudden or slow onset of human diabetes can be imitated in dogs. Several interesting examples of apparent onset after traumatism have occurred, in which it is evident that the trauma merely made active a latent diabetes. This does not exclude the possibility that trauma alone may sometimes cause diabetes in man, any more than the absence of any observed association between diabetes and infection in dogs contradicts the demonstrated facts that infections aggravate human diabetes and that patients have been known to acquire diabetes with an infection and recover completely after the infection. The experiments prove that the ingestion of excessive carbohydrate or protein does not create diabetes but merely hastens its active onset. When the underlying tendency is slight enough, indulgence or avoidance of dietary excess may be a deciding factor. These, in conjunction with former experiments, make it seem probable that luxus consumption of carbohydrate, nerve-strain, and other controllable influences may affect the incidence of diabetes by bringing out latent diabetic tendencies in a population.

The investigation of the rôle of fat in relation to glycosuria was undertaken along several lines. The proportion of pancreas

which must be removed to induce diabetes in fat and thin [2] dogs cannot be shown to differ beyond the limits of experimental error and individual variation. The essential experiments consisted in depancreatizing dogs so that severe diabetes came on with or without overfeeding, and proving that the glycosuria could be stopped by fasting and kept absent on low diet at subnormal weight, while addition of fat to the diet brought on gain of weight and consequent glycosuria. These were the experiments upon which the undernutrition treatment was founded. The requirement was to make them conclusive. Accidental factors must be excluded, and it must be established whether the downward progress of such dogs is prevented or merely delayed. One possible method is to compare a sufficient series of undernourished dogs with the well-nourished dogs and learn which live longest and how the tolerance behaves. This was done, and in several undernourished animals a gratifying improvement of protein assimilation was observed, in contrast to the downward tendency in the controls. But the undernourished animals fell victims to laboratory environment, and the attempt had to be repeated. The longest duration was one year, with continued gain in tolerance and strength, which is not without importance. The undernourished state cannot be blamed for causes of death such as rabies, and badly undernourished street curs appear hardy. But in consequence of the accidents, none of these experiments were long enough to found a fully decisive comparison. The ideal procedure would be to keep dogs sugar-free for a period on a given diet, then fatten the same dogs by adding only fat to the diet and show that glycosuria ensues, and then remove or diminish the fat and prove that glycosuria ceases and tolerance is raised. These experiments also were long, and were carried to the point where the obese dogs developed glycosuria. These were the first deaths in coma, which were important in opening up the study of acidosis, but highly inconvenient in the present connection through spoiling the chance of showing that the identical animals

[2] "Thin," in the ordinary sense, opposed to obese. Long fasting or extreme undernutrition makes a decided difference.

could be free from diabetes at reduced weight. On the whole the experiments along these lines were of a difficult and disappointing character, such as one would not wish to go through with again. Large pancreas remnants were requisite, in order that the dogs might retain appetite and digestion for fat. Animals must be chosen voracious enough to take hundreds of grams of sugar to break down their tolerance, and later to consume enough fat with restricted protein to become obese, as most dogs will not do. The preparatory period of sugar-freedom and fixing the tolerance was tedious, and after some months the dog might refuse to eat enough for fattening and have to be used for some other purpose. Few laboratories could be expected to repeat such experiments, and the outcome would still be subject to a personal factor. The results of briefer tests were in apparent contradiction to the longer experiments. Addition of fat to a diet causes a distinct depression of blood-sugar during digestion, confirming Jacobsen's findings in human patients. Dog 386 gives an example; Table VIII shows how the blood-sugar was lower in every instance on protein plus fat than on the same quantity of protein alone. Intravenous glucose injections do not occasion higher glycosuria during alimentary lipemia than during fasting. The reports of Blum and Roubitschek that fat feeding increases adrenalin glycosuria could not be confirmed. The first part of the record of dog 356 (Table V) shows how feeding of only suet diminished the hyperglycemia in an animal with potentially severe diabetes. Even in the severest active diabetes the feeding of pure fat does not increase hyperglycemia or glycosuria. This statement is not altered by the experience that under some circumstances dogs with severe diabetes show a striking increase of blood-sugar after receiving fat; but though this increase may continue for several hours it may begin almost immediately, therefore is obviously not due to anything derived from the fat; and this view was confirmed by finding that an equal amount of kaolin or talcum powder has the same effect. It will be noticed that all the experiments of this order are inimical to the idea of sugar formation directly from fat. In the face of all the uncertainties and contradictions, there was a distinct belief that the long ex-

DOG 386 (PARTIALLY DEPANCREATIZED)
LUNG AND SUET DIET
KGMS BODY WEIGHT
14
PLASMA SUGAR
%
.30
13
.25
12
BODY WEIGHT
11
.20
PLASMA SUGAR
.15
.10
.05
FED 77 GMS PROTEIN
SEPT. 5, 1916
URINARY SUGAR 0
FED 77 GMS PROTEIN 100 GMS FAT
SEPT. 6, 1916
URINARY SUGAR 0
FED 154 GMS PROTEIN
SEPT. 8, 1916
URINARY SUGAR 0
FED 154 GMS PROTEIN 100 GMS FAT
SEPT. 10, 1916
URINARY SUGAR 0
FED 77 GMS PROTEIN 120 GMS FAT
SEPT. 27, 1916
URINARY SUGAR 0
FED 77 GMS PROTEIN
SEPT. 28, 1916
URINARY SUGAR 0
FED 75 GMS PROTEIN 200 GMS FAT
OCT. 7, 1916
URINARY SUGAR 0
FED 75 GMS PROTEIN
OCT. 9, 1916
URINARY SUGAR 0
FED 75 GMS PROTEIN 200 GMS FAT
OCT. 17, 1916
URINARY SUGAR 0
FED 75 GMS PROTEIN
OCT. 18, 1916
URINARY SUGAR
FED 75 GMS PROTEIN
NOV. 7, 1916
URINARY SUGAR 0
HOURS 0 1 2 3 4 5 0 1 2 3 4 5 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8 0 2 4 6 8

TABLE VIII

periments pointed to fat feeding as a potent factor for producing diabetic glycosuria; but the question remained how to make this a positive conclusion instead of a personal impression.

Two changes were introduced. First, a slight increase in the staff permitted following the blood-sugar more satisfactorily. Second, independence of the dog's caprice was gained by forcible feeding when necessary. The appetite of diabetic patients has never been the guide to their diet. Fat has been given to them disguised by all the arts of cookery, and in addition they have been ordered to drink olive oil and otherwise consume fat beyond their desire. It has not been found possible to fool the instincts and senses of dogs when they begin to revolt at fat, but it is feasible to stuff down a ration exceeding what most dogs will continue to eat voluntarily, and if properly planned it is well digested and absorbed. Since the highest fat gives the quickest results, the experiments are thus compressed into a few weeks or months and are convenient to repeat. The numerous controls show the absence of any similar results in dogs not subjected to the fattening process. At the same time successful experiments in which greedy dogs ate everything voluntarily show that the forcible feeding is responsible for no difference; and earlier experiences (above described) prove that the same thing happens when the ration is more moderate, only the time required is longer. Two examples of the recent type of experiments are here shown.

Dog 356 (Table V) underwent operation on July 13, which left a remnant of one-eighth to one-ninth of the pancreas. The tolerance was broken down by feeding, so that it was slightly below one kilogram of lung; that is, on feeding this quantity, glycosuria remained absent until the third day, then was 2.85 per cent. It was cleared up by two days of fasting; then on August 21 a diet lower in protein but higher in calories was given, namely, 400 grams lung and 200 grams suet. This dog had been in barely medium condition at her original weight of 15 kilos. The preparatory stage had reduced her to 11 kilos. The greatly undernourished dog ate all the suet eagerly, and tolerated this excessive ration without glycosuria, until on

August 25 glycosuria of 2.6 grams appeared, with a fasting blood-sugar of 0.2 per cent. Here lung was omitted, and 400, then 300, then 200 grams of suet fed. Under this huge caloric intake, glycosuria ceased and the blood-sugar rapidly fell, giving no sign of sugar formation from fat. The protein was then cut far below the tolerance, and the fat diminished to what the dog could digest regularly. The normal plasma sugars from September 6 to 11 show that this diet of 150 grams lung and 200 grams suet was well within the tolerance at that time. Weight was steadily gained and the blood-sugar rose in parallel, while ketonuria and lipemia developed. The plasma sugar values on September 28 and 29 without glycosuria illustrate the renal impermeability under these conditions. On September 30 glycosuria developed. The diet at this time was changed to 200 grams lung, being approximately the former protein intake with omission of fat; and it was hoped that the course might thus be changed for the better. But the evil that fat does lives after it. A patient threatened with coma may not necessarily clear up if given a protein ration such as he subsequently may come to tolerate well after fasting; and when the injurious effect of fat has been pushed to this extreme point in diabetic dogs they are narrowly saved by using the same treatment as for human patients, although if the program had been changed earlier the simple omission of fat might suffice to reverse the progress. Accordingly, this dog was promptly fasted and there was prompt cessation of glycosuria and ketonuria. Low diet changed the condition so that the weight on November 3 was only 8.15 kilos, and 200 grams lung without fat caused no glycosuria, though the plasma sugar was 0.2 per cent., showing this ration to be still excessive. This is an example of treatment of severe diabetes by marked undernutrition. When the dog was four kilos below medium weight, the attempt to fatten her up to 3 kilos below the weight precipitated a dangerous diabetic outbreak, even though the gain was accomplished by addition of pure fat and there is no indication that sugar is formed from the fat. Not the kind of food given, but precisely the gain in weight above what the assimilative function is able to carry, is the cause of the breakdown in such dogs and

in corresponding human patients. Life is saved by reducing the body mass to what the assimilative power is able to maintain, and if the sparing is adequate, more or less recovery of the function follows in all dogs and in the great majority of human patients. Such an undernourished state as required in this animal, though unpleasant in dog or man, affords the sole means available not only for averting impending death but also for opening the way to a better state. The diabetic has not the choice of a short and merry life versus a long and miserable one. By overtaxing his assimilation he brings on both shortness and misery of existence. These very thin dogs are stronger and happier than the fatter animals with glycosuria and acidosis; and the treatment of fasting and undernutrition for patients has brought not only improvement from the standpoint of laboratory analyses and expectation of life, but also comfort and usefulness and freedom from a multitude of complicating afflictions to a degree never before known.

In other animals as thin as this and with an equally low tolerance, in which the breakdown was produced by carbohydrate or protein, treatment by undernutrition has resulted in steady improvement, as manifested by ability to endure more food and more weight up to a necessary limit. Injury from fat is more lasting and dangerous, presumably because less obvious, so that the harmful process is at work unseen for a considerable time before treatment is applied. This dog 356 finally died in extreme emaciation after a course apparently representing spontaneous downward progress. It furnishes an exact parallel to the type of patients who finally die in spite of treatment, through failing to gain enough assimilative function to support life.

The graphic record of dog 386 (Table VIII) gives a different example of the same principle. The dog came to the laboratory fat at a weight of 15 kilos, and the operation on April 28 left a remnant of only one-twelfth to one-thirteenth of the pancreas. Thus the tendency to diabetes was made more pronounced than in the preceding dog; but in consequence of more careful diet, for a longer period, the actual assimilation and condition were better. The tolerance was approximately 800 grams lung, which

caused slight glycosuria on August 10, when the dog weighed 11.8 kilos, and no glycosuria on September 15, when the weight was about a kilo less. Meanwhile the regular diet was 400 grams lung, which was tolerated for a month without a trace of glycosuria. On September 18 the diet was changed to 350 grams lung and 150 to 250 grams suet, which was continued except for a few test days for just a month. The animal behaved splendidly, enjoyed the diet throughout, and permitted a flawless experiment. The chart shows that at the outset the only indication of severe diabetes in a dog which seemed so beautifully healthy was the fact that protein feeding caused regularly a rise of blood-sugar like that produced by a large amount of carbohydrate normally. This is an interesting peculiarity of such animals. Not only the 400 grams of lung on September 5 and 6 was well borne, but also the 800 grams on September 15 and 16 caused no hyperglycemia greater than 0.13 per cent., thus proving the assimilation. Then the fat was added to the diet and the weight progressively rose. The chart shows how the fasting values for the plasma sugar were constantly within normal limits on the protein diet, also that where the plasma sugar was determined hourly or two-hourly after feeding, the curve after protein plus fat was invariably lower than after the same quantity of protein alone. Nevertheless, as the weight rose the sugar curves also rose. On October 17 the regular protein-fat diet did not suffice for glycosuria, but on the next day the simple omission of the fat sent the plasma sugar so much higher that a glycosuria of 1.21 grams resulted. The attempt to carry this experiment through without fasting was unsuccessful, but on the usual treatment the glycosuria and the ketonuria also present promptly cleared up. On a low diet of protein the weight was brought down to 11.7 kilos, and a test on November 3 showed a fasting plasma-sugar of only 0.1 per cent. which rose only to 0.118 per cent. without glycosuria on the identical protein intake as before. As stated, the operatively produced tendency to diabetes is greater in this dog than in dog 356, but this one represents a case taken before it is so far advanced. This animal can be kept healthy and happy at as high a weight as necessary for either strength

or symmetry. Obesity would bring on diabetes irrespective of the kind of food that produced the obesity.

In these and similar experiments one incidental observation is that the blood-sugar is not an infallible criterion for prognosis. It may be within normal limits both before and after meals on a diet which nevertheless is destined to make trouble later. Also, a very high level of blood-sugar may persist for a considerable time after wiser treatment has changed the direction of progress, so that hyperglycemia does not of itself demonstrate a breaking strain of assimilation or preclude improvement. A more broadly important lesson is that the age-long search of chemists for a magic food which diabetics shall assimilate perfectly is as vain as earlier quests of the holy grail or the fountain of youth or the philosopher's stone. What the diabetic organism is unable to assimilate without restriction is not any particular kind of food, but food as such. From this standpoint all the attempts from the earliest ones with glycerin and lactic acid and levulose down to Rosenfeld's lactone and Grafe's caramel may be judged together and the true reason of their failure appreciated. It is not necessary to conclude that any component of fat is changed into sugar. Although Cremer and Lüthje proved the formation of sugar from glycerin, von Mering first and Lusk more exactly showed that fat feeding does not affect phloridzin glycosuria, and the latter found further that work, which increases fat catabolism, does not alter the D:N ratio, so there is entire lack of evidence that glycerin is split off from fat to form sugar. It may be significant that the experiments and theories of Embden, Neuberg, Dakin, Ringer and Woodyatt, however differing in details, stand in agreement regarding the conception of a merging and equilibrium of chemical products from different sources. It is known that certain substances participating in intermediary metabolism are chemically derivable from either protein, fat, or carbohydrate. Apart from the actual interconversion on a large scale possible between some of these substances, as amino-acids and sugar, it is conceivable that the mere glut of any products is a hindrance to either the anabolism or the katabolism of other products. In such embarrassment of the cells there are certain

substances which most readily escape into the blood and urine; but it must not be concluded from this fact that the diabetic fault of assimilation is limited to sugar (as apparently in phloridzin poisoning) or that the intoxication of acidosis is merely due to the acetone bodies. Wells near the seashore rise and fall with the tide, not because any fresh water is derived from the ocean, but because the drainage of the underground streams is blocked in proportion as the tide is high. Such a comparison may explain the production of diabetic glycosuria by fat for those who do not believe in the derivation of sugar from fat. The primarily ketogenetic and secondarily glycosuric action of fat and the primarily glycosuric and secondarily ketogenetic action of carbohydrate are in accord with this speculation. Janney's investigations of proteins cannot show that any amino-acids are harmless, but may indicate which of them are preferable in cases in which the principal immediate tendency is to glycosuria and in others in which the existing tendency is to acidosis.

The most important fact shown by this series of experiments is that the appearance of spontaneous downward progress observed in human patients can be exactly imitated in dogs. It is possible that further factors, notably occasional infections, may be operative in at least some human cases. It is not positive that the undernourished dogs will be able to live indefinitely. But it is conclusively demonstrated that the attempt at high nutrition, even with fat, produces in these dogs an appearance of spontaneous aggravation of condition as striking as anything witnessed in human patients, and that this result can be prevented at least for periods of years by limiting the total caloric intake and the body mass to correspond to the assimilative function. The experience with diabetic dogs warns unmistakably against efforts to maintain patients on a luxus level of diet or weight. The standard should approach that of Chittenden rather than that of Voit. Restriction of single foods, as carbohydrate or protein, suppresses symptoms temporarily, but lightening the total load upon the weakened assimilative function is the only present means by which it may be hoped actually to halt the diabetic process.

The animal experiments have placed the successful therapeutic

results on something more substantial than an empiric basis, independent of opinions or impressions, and no clinical mishaps, whether due to faulty application of the method or to failure of a defective function to recover by rest, can now shake the principles on which this treatment is founded or justify a return to overfeeding with fat and other mistakes of the past.

BIBLIOGRAPHY

Allard, E.: Arch. f. exp. Path. u. Pharm, 1908, lix, 388–396. Die Acidose beim Pankreasdiabetes.

Allen, F. M.: Glycosuria and Diabetes. Harvard University Press, 1913.

Almagia, M., and Embden, G.: Hofmeister's Beiträge, 1905, vi, 59–62. Ueber das Auftreten einer flüchtigen, jodoformbildenden Substanz bei der Durchblutung der Leber.

Aschoff, L.: Ziegler's Beiträge z. path. Anat. u. allg. Path., 1909, xlvii, 1. Zur Morphologie der lipoiden Substanzen.

Bacmeister: Biochem. Ztschr., 1910, xxvi, 223–230. Untersuchungen über Cholesterinausscheidung in meschlichen Gallen.

Baer, J.: Arch. f. exp. Path. u. Pharm., 1904, li, 271–288. Die Acidose beim Phlorhizindiabetes des Hundes. Ibid., 1906, liv, 153–167. Ueber das Verhalten verschiedener Säugetierklassen bei Kohlehydratentziehung.

Bauer, J.: Wien. klin. Wchnschr., 1912, xxv, 1377–1380. Ueber das fettspaltende Ferment des Blutserums bei krankhaften Zuständen.

Benedict, F. G.: Carnegie Institution of Washington, Publication No. 203, 1915, A study of prolonged fasting.

Benedict, S. R., and Osterberg, E.: Proc. Soc. Exp. Biol. and Med., 1914, xii, 45. The influence of feeding upon acidosis in the phlorhizinized dog.

Beumer, H., and Bürger, M.: Ztschr. exp. Path. u. Ther., 1913, xiii, 343–361. Beiträge zur Chemie des Blutes in Krankheiten mit besonderer Berücksichtigung der Lipoide III. Ibid., 263–366. Beiträge zur Chemie des Blutes in Krankheiten mit besonderer Berücksichtigung der Lipoide. IV. Diabetes und Lipämie.

Bleibtreu, M.: Pflüger's Arch., 1901, lxxxv, 345–400. Fettmast und respiratorischer Quotient.

Bloor, W. R.: Jour. Biol. Chem., 1913–14, xvi, 517–529. On fat absorption. III. Changes in fat during absorption. Ibid., 1914, xvii, 377–384. A method for the determination of fat in small amounts of blood. Ibid., 1914, xix, 1–24. Studies on blood fat. I. Variations in the fat content of the blood under approximately normal conditions. Ibid., 1915, xxiii, 317–326. Studies on blood fat. II. Fat absorption and

the blood lipoids. Ibid., 1916, xxv, 577–599. The distribution of the lipoids ("fat") in human blood. Ibid., 1916, xxvi, 417–430. The lipoids ("fat") of the blood in diabetes.

Blum, F.: Pflüger's Arch., 1902, xc, 617–629. Weitere Mittheilungen zur Lehre von dem Nebennierendiabetes.

Blum, L.: München. med. Wchnschr., 1910, lvii, 683–685. Ueber den Abbau von Fettsäuren im Organismus und über die gegenseitigen Beziehungen der Azetonkörper.

Boggs, T. R., and Morris, R. S.: Jour. Exper. Med., 1909, xi, 553–560. Experimental lipemia in rabbits.

Bönniger, M., and Mohr, L.: Ztschr. exp. Path. u. Ther., 1906, iii, 675–687. Untersuchungen über einige Fragen des Hungerstoffwechsels. I. Die Säurebildung im Hunger.

Borberg, N. C.: Skand. Arch. f. Physiol., 1915, xxxii, 287–351. Zur Biochemie der Lipoiden.

Brugsch: Ztschr. exp. Path. u. Ther., 1905, i, 419–430. Eiweisszerfall und Acidosis in extremen Hunger mit besonderer Berücksichtigung der Stickstoffvertheilung im Harn.

Caro, L.: Ztschr. klin. Med., 1913, lxxviii, 286–293. Fettspaltende Fermente im menschlichen Blutserum, ihre Abhängigkeit von krankhaften, namentlich kachektischen Zuständen, ihre Unabhängigkeit von der histologischen Zusammensetzung des Blutes.

Chauffard, C.: Compt. rend. Soc. biol., 1911, lxx, Ibid., 1912, lxxiii. Semaine méd., 1912, No. 17.

Connstein, W.: Ergebnisse der Physiologie, 1904, iii, Abt. 1, 194–232. Ueber fermentative Fettspaltung.

Cremer, M.: München. med. Wchnschr., 1902, 944. Entsteht aus Glyzerin und Fett im Körper des höheren Thieres Traubenzucker? Sitzungsb. d. Gesellsch. f. Morphol. u. Physiol. in München., 1902, H. 2. Ref. in Maly's Jahresb., 1903, xxiii, 604–606.

Dakin, H. D.: Jour. Biol. Chem., 1910–11, viii, 97–104. The formation in the animal body of 1-β-oxybutyric acid by the reduction of acetoacetic acid. A contribution to the study of acidosis.

Dakin, H. D., and Dudley, H. W.: Jour. Biol. Chem., vols. xiv, xv, and xviii.

Ehrmann, R.: Berl. klin. Wchnschr., 1913, 11–14, 65–67. Ueber das Coma diabeticum.

Embden, G.: Hofmeister's Beitr., vols. viii and xi. Verh. d. deutsch. Kong. f. inn. Med., 1907, xxiv, 252–255. Beitrag zur Lehre von der Acetonurie.

Erben, F.: Ztschr. f. klin. Med., 1900, xl, 266–281. Die chemische Zusammensetzung des Blutes bei perniciöser Anämie. Ibid., 282–293. Zur Kenntniss der chemischen Zusammensetzung lymphämischen Blutes.

Ewing, J.: Archives of Int. Med., 1908, ii, 330–354 and 448–503. Acidosis and associated conditions.

Fischer, B.: Virchows Arch., 1903, clxxii, 30–71 and 218–261. Ueber Lipämie und Cholesterämie, sowie über Veränderungen des Pankreas und der Leber bei Diabetes mellitus.

Fischler, F., and Kossow, H.: Deutsch. Arch. klin. Med., 1913, cxi, 479–502. Vorläufige Mitteilung über den Ort der Acetonkörperbildung nach Versuchen mit Phlorrhizin an der partiell ausgeschalteten Leber nebst einigen kritischen Bemerkungen zur sog. Fleischintoxikation beim Eck'schen Fistelhunde.

Folin, O.: Laboratory Manual of Biological Chemistry, 1916.

Folin, O., and Denis, W.: Jour. Biol. Chem., 1914, xviii, 263–271. Turbidity methods for the determination of acetone, aceto-acetic acid and β-oxybutyric acid in urine. Ibid., 1915, xxi, 183–192. On starvation and obesity, with special reference to acidosis.

Forssner, G.: Skand. Arch. f. Physiol., 1909, xxii, 349–392. Ueber die Einwirkung des Nahrungsfettes auf die Acetonkörperausscheidung.

Freund, E., and Obermayer, F.: Ztsch. f. physiol. Chem., 1891, xv, 310–318. Ueber die chemische Zusammesetzung leukämischen Blutes.

Frugoni, C., and Marchetti, G.: Berl. klin. Wchnschr., 1908, xlv, 1844–1846. Beitrag zum Studium der diabetischen Lipoidämie.

Gardner, J. A., and Lander, P. E.: Biochemical Journal, 1913, vii, 576–587. On the cholesterol content of the tissues of cats under various dietetic conditions and during inanition.

Geelmuyden, H. Chr.: Ztschr. physiol. Chem., 1897, xxiii, 431–475. Ueber Aceton als Stoffwechselprodukt. Skand. Arch. Physiol., 1901, xi, 97–122. Untersuchungen über Acetonkörper.

Gerhardt, D., and Schlesinger, W.: Arch. exp. Path. u. Pharm., 1899, xlii, 83–108. Ueber die Kalk-und Magnesiaausscheidung beim Diabetes melitus und ihre Beziehung zur Ausscheidung abnormer Säuren (Acidose).

Gigon, A.: Ergebn. d. inn. Med. u. Kinderheilk., 1912, ix, 284–299. Neuere Diabetesforschungen.

Ginsberg: Archiv f. Ophthalmol., Bd. lxxxii, H. 1, Ref. by Klinkert.

Grafe, E.: München, med. Wchschr., 1914, lxi, 1433–1437. Ueber Karamelkuren bei Diabetikern. Deutsch. Arch. klin. Med., 1914, cxvi, 437–460. Ueber die Wirkung des Karamels im normalen und diabetischen Organismus.

Gumprecht: Deutsch. med. Wchnschr., 1894, xx, 756–757. Ueber Lipämie.

Hallervorden, E.: Arch. f. exp. Path. u. Pharm., 1880, xii, 237–275. Ueber Ausscheidung von Ammoniak im Urin bei pathologischen Zuständen.

Hirschfeld, F.: Ztschr. f. klin. Med., 1895, xxviii, 176–209. Beobachtungen über die Acetonurie und das Coma diabeticum.

Howland, J., and Marriott, W. McK.: Proc. Soc. Exp. Biol. and Med., 1914, xii, 51–54. Observations upon the so-called food intoxication of infants with especial reference to the alveolar air. Abstract of the

Proceedings of the Seventh Annual Meeting of the American Society for the Advancement of Clinical Investigation, 1915, pp. 18–22. Study of acidosis occurring in the nutritional disturbances of infancy. Abstract of Proceedings of Eighth Annual Meeting of the American Society for Clinical Investigation, 1916, 23–25. Factors in the production of acidosis in nephritis. Bull. Johns Hopkins Hosp., 1916, xxvii, 63–69. A discussion of acidosis, with special reference to that occurring in diseases of children.

Hurtley, W. H.: Quart. Jour. Med., 1916, ix, 301–408. The four carbon atom acids of diabetic urine.

Imrie, C. G.: Jour. Biol. Chem., 1915, xx, 87–90. On the fat in the blood in a case of lipemia.

Jacobsen, A. Th. B.: Biochem. Ztsch., 1913, lvi, 471–494. Untersuchungen über den Einfluss verschiedener Nahrungsmittel auf den Blutzucker bei normalen, zuckerkranken und graviden Personen.

Janney, N. W.: Jour. Biol. Chem., 1915, xx, 321–350. Metabolic relationship of the proteins to glucose. Arch. Int. Med., 1916, xviii, 584. Glucose formation from protein in diabetes.

Jastrowitz, H.: Ztsch. exp. Path. u. Ther., 1914, xv, 116–166. Ueber Lipoidverfettung.

Kawamura, R.: Virchows Arch., 1912, ccvii, 469–476. Die Cholesterinesterverfettung der Kupfferschen Sternzellen.

Kirk, E. G.: Arch. Int. Med., 1915, xv, 38–76. The relation of pancreatic organotherapy to ketogenesis.

Klinkert, D.: Berl. klin. Wchnschr., 1913, 1, 820–825. Untersuchungen und Gedanken über den Cholesterinstoffwechsel.

Kreidl, A., and Neumann, A.: Sitzungsber. d. k. Wien. Akad. d. Wissenschaften, math. naturwiss. Klasse, 1911, cxx. Abt. 3, 127–138. Ueber die Fettresorption bei Katzen und Kaninchen nach Blutuntersuchungen im Dunkelfeld.

Krumbhaar, E. B.: Jour. Exper. Med., 1916, xxiv, 361– 365. Spontaneous diabetes in a dog.

Landau, M.: Deutsch. med. Wchnschr., 1913, 546–549. Nebenniere und Fettstoffwechsel.

Lattes, L.: Arch. exp. Path. u. Pharm., 1911, lxix, 132–142. Ueber den Fettgehalt des Hundes unter normalen und unter verschiedenen experimentallen Verhältnissen (Verdauung, Hungern, Phosphor-, Phloridzin- und Chloroformvergiftung).

Lauber and Adamuck: Arch. f. Ophthalmol., 1909, lxxi, 429. Ref. by Klinkert.

Lehman, E. P.: Jour. Biol. Chem., 1913–14, xvi, 495–503. On the rate of absorption of cholesterol from the digestive tract of rabbits.

Levy, R. L.:, Rowntree, L. G., and Marriott, W. McK.: Arch. Int. Med.,

1915, xvi, 389–405. A simple method for determining variations in the hydrogen-ion concentration of the blood.

Lewis, R. C., and Benedict, S. R.: Jour. Biol. Chem., 1915, xx, 61–72. A method for the estimation of sugar in small quantities of blood.

Lusk, G.: Ztschr. f. Biol., 1901, xlii, 31–44. Ueber Phlorhizin-Diabetes. Arch. Int. Med., 1909, iii, 1–22. Metabolism in diabetes.

Lusk, G., Reilly, F. H., and Nolan, F. W.: Am. Jour. Physiol., 1898, i, 395–410. Phlorhizin diabetes in dogs.

Lüthje, H.: Deutsch. Arch. klin. Med., 1904, lxxx, 98–104. Die Zuckerbildung aus Glyzerin. München. med. Wchnschr., 1902, xlix, 1601–1603. Zur Frage der Zuckerbildung im tierischen Organismus.

Maase, C.: Med. Klinik., 1910, lxi, 445–445. Ueber eine neue Bildungsweise der β-oxybuttersäure.

Magnus-Levy, A.: Arch. exp. Path. u. Pharm., 1901, xlv, 389-434. Untersuchungen über die Acidosis im Diabetes melitus und die Säureintoxication im Coma diabeticum. Ergebn. d. inn. Med. u. Kinderheilk., 1908, i, 352–419. Die Acetonkörper.

Magnus-Levy, A., and Mayer, L. F.: Vol. iv, Carl Oppenheimer's Handbuch der Biochemie des Menschen und der Tiere, Jena, 1911; 445–488. Die Fette im Stoffwechsel.

Marriott, W. M.: Jour. Biol. Chem., 1913–14, xvi, 293–8. The determination of β-oxybutyric acid in blood and tissues. Ibid., 1914, xviii, 241–262. The metabolic relationships of the acetone substances. Ibid., 1914, xviii, 507–517. The blood in acidosis from the quantitative standpoint. Jour. Am. Med. Assn., 1914, lxiii, 397–398. The blood in acidosis from the quantitative point of view.

McLean, F. C.: Jour. Exper. Med., 1915, xxii, 366–388. The numerical laws governing the rate of excretion of urea and chloride in man. II. The influence of pathological conditions and of drugs on excretion.

Mendel, L. B.: Jour. Biol. Chem., 1914 and 1915.

Minkowski, O.:: Arch. exp. Path. u. Pharm., 1893, xxxi, 214–221. Ueber die Ursachen der Milchsäureausscheidung nach der Leberexstirpation.

Mohr, L.: Sammlung klinischen Abhandlungen über Pathologie und Therapie der Stoffwechsel- und Ernährungsstörungen, Berlin, 1904, H. 4. Ueber diabetische und nicht-diabetische Autointoxicationen mit Säuren (Acidosis).

Müller, J.: Ztschr. physiol. Chem., 1913, lxxxvi, 469–483. Ueber Maskierung des Blutfettes und der Blutlipoide sowie über Verdauungslipämie beim Menschen.

Mulon, P.: Compt. rend. Soc. biol., 1913, lxxv, 189–192. Disparition des enclaves de cholestérine de la surrénale au cours de la tétanisation faradique ou strychnique.

Munk, J., and Friedenthal: Centralbl. f. Physiol., 1901, xv, 297. Resorption des Nahrungsfettes nach Unterbindung des Ductus thoracicus.

Munk, J.: Arch. f. Physiol., 1890, 116–141. Ueber die Wirkungen der Seifen im Thierkörper.

Murlin, J. R., and Lusk, G.: Jour. Biol. Chem., 1915, xxii, 15–41. Animal Calorimetry, XII. The influence of the ingestion of fat.

Murlin, J. R., and Riche, J. A.: Proc. Soc. for Exp. Biol. and Med., 1915, xiii, 7–8. Blood fat in relation to heat production and depth of narcosis. Proc. Amer. Physiol. Soc., December, 1915. Am. Jour. Physiol., 1916, xl, 146. The fat of the blood in relation to heat production, narcosis and muscular work.

Naunyn, B., Leyden-Klemperer: Deutsche Klinik, 1902, iii. Der Diabetes melitus. Der Diabetes melitus, Wien, 1906, p. 271.

Neisser, E., and Braeuning, H.: Ztschr. f. exp. Path. u. Ther., 1917, iv, 746–760. Ueber Verdauungslipämie.

Neisser, E., and Derlin, L.: Ztschr. f. klin. Med., 1904, li, 428–438. Ueber Lipämie.

Nerking, J.: Pflüger's Arch., 1901, lxxxv, 330–344. Ueber Fetteiweissverbindungen.

Neubauer, O.: Abderhalden's Handbuch der biochemischen Arbeitsmethoden, 1912, Part 2, v, 1216–1217.

Neuberg: Biochem. Ztschr., 1915, lxxi.

Porges, O.: Ergebn. d. Physiol., 1910, x, 1–46. Ueber den Abbau der Fettsäuren im Organismus.

Porges, O., and Novak, J.: Berl. klin. Wchnschr., 1911, xlviii, 1757–1760. Ueber die Ursache der Acetonurie bei Schwangeren.

Raulston, B. O., and Woodyatt, R. T.: Jour. Am. Med. Assn., 1914, lxii, 996–999. Blood transfusion in diabetes mellitus.

Reicher, K.: Ztschr. klin. Med., 1908, lxv, 235–268. Chemisch-experimentelle Studien zur Kenntnis der Narkose. Verh. d. deutsch. Kong. f. inn. Med., 1911, xxviii, 327–330. Zur Kenntnis des Fett- und Lipoidstoffwechsels.

Riesman, D.: Jour. Am. Med. Assn., 1916, lxvi, 85. Soft eyeball in diabetic coma.

Ringer, A. I., and collaborators: Jour. Biol. Chem., vols. xiv, xv, xvii, xviii.

Rolly, Fr.: Med. Klinik, 1913, ix, 568–572. Das Wesen und die Behandlung des Coma diabeticum.

Rona, P., and Michaelis, L.: Biochem. Ztschr., 1911, xxxi, 345–354. Ueber Ester- und Fettspaltung im Blute und im Serum.

Rosenbloom, J.: Jour. Am. Med. Assn., 1915, lxv, 1715–1716. The acetone bodies in diabetes mellitus.

Rosenfeld, G.: Centralbl. f. inn. Med., 1895, xvi, 1233–1244. Die Grundgesetze der Acetonurie und ihre Behandlung. Berl. klin. Wchnschr., 1906, xliii, 978–981. Fett und Kohlenhydrate.

Rothera, A. C. H.: Jour. Physiol., 1908, xxxvii, 491–494. Note on the sodium nitroprusside reaction for acetone.

Roubitschek, R.: Pflüger's Arch., 1914, clv, 68–76. Zur Frage der Zuckerbildung aus Fett.

Sakai, S.: Biochem. Ztschr., 1914, lxii, 387–445. Zur Pathogenese der Lipämie.

Sass, M.: Ztschr. exp. Path. u. Ther. 1914, xv, 370–378. Die Aenderung der Blutalkalescenz beim Pankreasdiabetes unter dem Einfluss von Muckelkrämpfen.

Schütz, E.: Ztschr. physiol. Chem., 1894, xix, 482–487. Ueber das Vorkommen von Fleischmilchsäure in pathologischen Harnen.

Sellards, A. W.: Johns Hopkins Hosp. Bull., 1914, xxv, 101–112. A clinical method for studying the titratable alkalinity of the blood and its application to acidosis.

Seo, Y.: Arch. exp. Path. u. Pharm., 1909, lxi, 1–6. Ueber das Vorkommen von Lipämie und über die Menge der Lipoidsubstanzen in Blut und Leber beim Pankreasdiabetes.

Stadelmann, E.: Arch. f. exp. Path. u. Pharm., 1883, xvii, 419–444. Ueber die Ursachen der pathologischen Ammoniakausscheidung beim Diabetes mellitus und des Coma diabeticum.

Taylor, A. E.: University of California Publications, Pathology, No. 7, i, 71–86. Studies on an ash-free diet. Digestion and Metabolism, Lea and Febiger, 1912.

Terroine, E. F.: Jour. de physiol. et de path. gén., 1914, xvi, 386–397. Variations lipo-cholestérinémiques au cours de l'inanition et de l'alimentation.

Thiroloix, J., and Jacob, P.:: Bull. et mém. de la Soc. méd. des hôp. de Paris, 1910, xxix, 492–494; 1910, xxx, 29–31, 656–658. Compt. rend. Acad. Sci., February 5, 1912, cliv.

Tyson, J.: A Treatise on Bright's Disease and Diabetes, Philadelphia, 1881.

Underhill, F. P.: Jour. Biol. Chem., 1913, xv. Studies on the metabolism of ammonium salts. Jour. Biol. Chem., vols. x, xvii, xx (Hydrazine).

Van Slyke, D. D.: Proc. Soc. Exp. Biol. and Med., 1916, xiii, 134. Gravimetric determination of beta-oxybutyric acid.

Van Slyke, D. D.: Stillman, E., and Cullen, G. E.: Proc. Soc. Exp. Biol. and Med., 1915, xii, 165–166. The nature and detection of diabetic acidosis. (Also forthcoming publication in Jour. Biol. Chem.).

von Mering, J.: Ztschr. f. klin. Med., 1888, xiv, 405–423. Ueber Diabetes mellitus. Ibid. 1889, xvi, 431–446. Ueber Diabetes mellitus.

von Noorden, C.: Handbuch der Pathologie des Stoffwechsels, Berlin, 1906, p. 533. Die Zuckerkrankheit, Berlin, 1912, p. 180.

Wakeman, A. J., and Dakin, H. D.: Jour. Biol. Chem., 1909, vi, 373–389. On the decomposition of β-oxybutyric acid and aceto-acetic acid by

enzymes of the liver. Ibid., 1910, viii, 105–107. On the decomposition of aceto-acetic acid by enzymes of the liver.

Waldvogel, R., and Hagenberg, J.: Ztschr. f. klin. Med., 1901, xlii, 443–450. Ueber alimentäre Acetonurie.

Walter, F.: Arch. exp. Path. u. Pharm., 1877, vii, 148–178. Untersuchungen über die Wirkung der Säuren auf den thierischen Organismus.

Weintraud, W.: Bibliotheca medica, 1893. Untersuchungen über den Stoffwechsel im Diabetes mellitus und zur diätetischen Therapie der Krankheit.

Woodyatt, R. T.: Jour. Am. Med. Assn., June 17, 1916, lxvi, 1910–1913. Acidosis in Diabetes. Jour. Biol. Chem., vols. xx, xxi, and xxiv. The Harvey Lectures, 1915–1916.

Zawilski: Arb. d. Leipz. physiol. Inst., 1876, 147. Ref. by Magnus-Levy and Meyer. Dauer u. Umfang d. Fettstromes durch d. Ductus thoracicus.

Zeller, H.: Arch. f. Anat. u. Physiol., Phys. Abt., 1914, 213–236. Einfluss von Fett und Kohlehydrat bei Eiweisshunger auf die Stickstoffausscheidung.