The Effects of Diabetic Acidosis and Coma Upon the Serum Lipoproteins and Cholesterol

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The disturbances of lipid metabolism induced by diabetic acidosis have been studied repeatedly since the pioneering work of Bloor.[1] Within the limitations of the chemical methods used, most workers have agreed that diabetic acidosis is generally characterized by chemical lipemia consisting principally of neutral fat, by hypercholesterolemia, and by a variable degree of lactescence of the separated serum.[2-9]

A preoccupation with the lipid metabolism of diabetic subjects is produced by three hypotheses. First, the conspicuous predilection of diabetic subjects to atherosclerosis, as well as other forms of arteriosclerosis, may be a consequence of transitory or continuing disorders of lipid metabolism. Second, the defect in lipid metabolism in diabetes mellitus may be even more basic to the disease than is generally appreciated. Third, the extreme deviations of lipid metabolism sometimes seen in diabetic acidosis may afford a profitable opportunity to investigate the physiological mechanisms for the transport of neutral fat or other lipids. The collaborative efforts of our laboratories have been directed primarily toward the first of these considerations.

The lipids in the blood are carried in the form of lipid-protein complexes. Gofman and his associates[10] studied some of these lipoproteins by an ultracentrifugal technic and found that they could be separated into various classes or bands, designated as S_f 0-11, 12-20, etc., depending upon the density of the molecule. The measurement of the kind and quantity of these lipoprotein classes in the serum gives an indication of the state of lipid metabolism.

In the present investigation, the disturbances of these serum lipoproteins and cholesterol were studied in a group of patients who entered the hospital in diabetic acidosis or coma. The dramatic effects of treatment of diabetic acidosis upon the lipoprotein complexes of serum are described, and the proposition is considered that the premature development of atherosclerosis may be related to these lipoprotein disturbances.

These studies were initiated after observation of a 16-year-old schoolboy who was brought to the hospital in diabetic coma. Physical examination revealed lipemia retinalis, and the serum was markedly lactescent. Routine treatment with insulin and saline followed by the usual dietary measures brought about a prompt clinical recovery. Serial laboratory measurements of the serum cholesterol, lipoproteins, blood sugar, and carbon dioxide were done and are summarized in Figure 1. The tran-

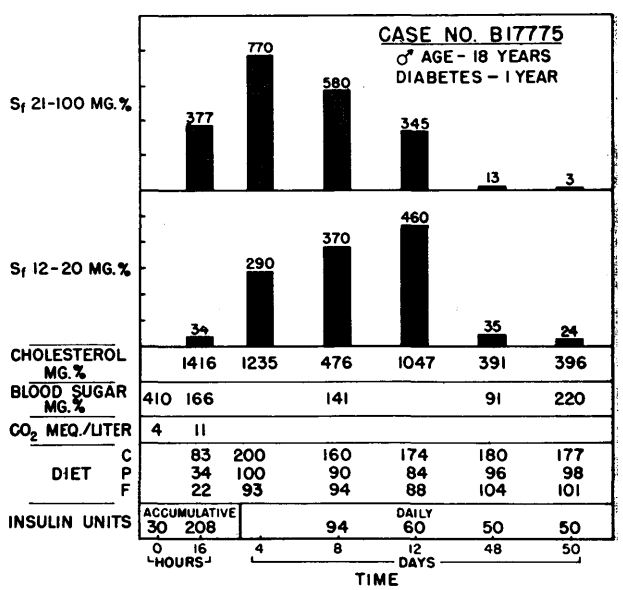

FIGURE 1. Serum lipoproteins and total cholesterol in a diabetic patient following an episode of diabetic coma.

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sient elevation of the S_f 12-20 lipoprotein band which occurred during the drop in values for the S_f 21-100 fraction, as well as the prolonged elevation above normal of both bands, excited considerable interest. A study was then planned to make similar observations in other patients.

METHODS

A total of 25 patients had two or more blood samples drawn for serial lipid determinations, although only 18 subjects were studied in sufficient detail to be considered here. Six of these were classified as being in diabetic acidosis (plasma carbon dioxide greater than 9 mEq./L.) and 12 were classified as diabetic comas (carbon dioxide less than 9 mEq./L.). The subjects studied were selected for various reasons of convenience and do not furnish a representative sample of the Clinic experience with respect either to prevalence or to any clinical characteristic of patients admitted in diabetic acidosis or coma.

The clinical care of these patients was carried out by the Joslin Clinic physicians according to their usual methods of management. The blood sugar and carbon dioxide measurements were obtained in the hospital clinical laboratory. The lipoprotein measurements were done by the methods of Gofman and others[10] and the serum total cholesterol by the methods of Abell and others.[11] Efforts were made to secure blood samples for lipid measurements on admission and at intervals thereafter during the patients' hospital stay and after discharge.

RESULTS

A clinical description and the initial laboratory findings of 18 patients admitted in diabetic acidosis or coma are given in Table 1 and Table 2. Although no precise correlation could be observed between blood sugar or carbon dioxide values and either cholesterol or lipoprotein values, a general relationship between the serum lipid deviation and the degree of acidosis was observed. In Figure 2, the initial plasma carbon dioxide is related to the S_f 21-100 and 100-400 fractions and to cholesterol. It may be seen that patients with coma showed somewhat greater elevations of serum lipid levels than did those admittted in acidosis. However, the scattering of the lipid values, particularly in the patients who were in coma, is large and probably indicates that other factors are affecting lipid metabolism.

In Figure 3 are presented the complete data obtained on four representative subjects. It is apparent from these data that the treatment of acidosis was characterized by rising CO_2 and by generally falling serum lipoprotein and cholesterol levels. However, it is also apparent that the values for cholesterol and for the various lipoprotein classes do not return toward normal at the same rate. It is also evident that in the interval of 24 to 48 hours following the initiation of oral feeding, the S_f 21-100 and 100-400 fractions show an increase in concentration. In some patients this increase has been maintained, and in others there has subsequently been a return to more normal values. It may also be noted that in certain of these young subjects treatment did not completely normalize the lipid transport system, for the S_f 0-11 band of lipoprotein and the serum cholesterol did not return to the levels expected in a person of that age and sex. These observations are discussed below in some detail.

DISCUSSION

In any discussion of the changes in concentration of components of the sera of diabetic patients under treatment for clinical acidosis or coma, it is important to consider the effect of the initial dehydration and the fluid therapy used to correct this. The patients described here received 3-5 liters of intravenous and oral fluid during the first 12-18 hours of treatment. Sufficient measurements to evaluate the state of hydration were not

TABLE 1
A clinical description of 18 subjects studied after admission in diabetic acidosis or coma

	Case No.	*Sex*	*Age (Years)*	*Years Duration of Diabetes*	*Previous Acidosis or Coma*	*Usual Insulin Required (Units)*
Acidosis	1	F	15	2	0	70
	2	M	14	11	+	40
	3	F	29	15	+	70
	4	M	32	29	0	50
	5	F	25	17	0	40
	6	M	19	10	0	100
Coma	7	F	16	5	0	62
	8	M	15	10	+	102
	9	F	15	0	0	32
	10	F	19	8	0	56
	11	F	28	4	0	40
	12	F	27	17	+	45
	13	F	44	23	0	40
	14	F	42	3	+	68
	15	M	34	1	0	56
	16	F	44	27	0	30
	17	F	26	7	+	52
	18	F	52	18	+	52

TABLE 2
The initial laboratory findings in 18 patients admitted in diabetic acidosis or coma

	Case No.	CO_2-mEq./L.	Blood Sugar Mg. per 100 cc.	Cholesterol Mg. per 100 cc.	Lipoprotein Mg. per 100 cc. S_f 0-11	S_f 12-20	S_f 21-100	S_f 100-400
Acidosis	1	15	200	276	310	120	232	24
	2	10	413	216*	120*	71	150	22
	3	12	393	233*	240*	62	95	0
	4	12	528	153*	120*	40	162	26
	5	15	934	299†	≥250*	143	129	5
	6	11	746	325*	≥300*	81	452	100
Coma	7	7	970	378‡	350‡	120	264	86
	8	3	697	327‡	≥230‡	110	390	180
	9	9	296	664	410	170	1420	≥400
	10	3	323	206	300	46	139	29
	11	8	267	330	220	88	450	160
	12	9	536	257	280	70	122	31
	13	5	556	414*	≥480*	130	368	170
	14	5	504	407*	≥450*	140	750	210
	15	4	990	399	≥300	112	361	63
	16	3	950	235	78	100	201	87
	17	3	600	364	≥300	54	70	14
	18	5	454	306	490	71	112	23

*Lipid values determined 2 hours after admission.
†Lipid values determined 4 hours after admission.
‡Lipid values determined 1 hour after admission.

The serum cholesterol and lipoprotein levels vary in normal individuals with sex and age. The S_f 0-10 class of lipoproteins constitutes the most abundant beta lipoprotein material in blood serum. The amount of this class of material correlates better with the serum total cholesterol than do the other classes of lipoprotein. The S_f 0-10 class concentration averages about 300 mg. per 100 cc. in adult human subjects and from 150 to 250 mg. per 100 cc. in children and adolescents. Little or no material of S_f 100-400 class of lipoproteins is contained in the sera of most normal subjects except for variable increases after a fatty meal. In males, S_f 12-20 values, expressed as averages of a group in each decade from 20 to 80 years of age, vary from 33 to 39 mg. per 100 cc. In females, similar values range from 24 to 39. Additional normal lipoprotein and cholesterol values are given by Keiding, Mann and their associates.[13]

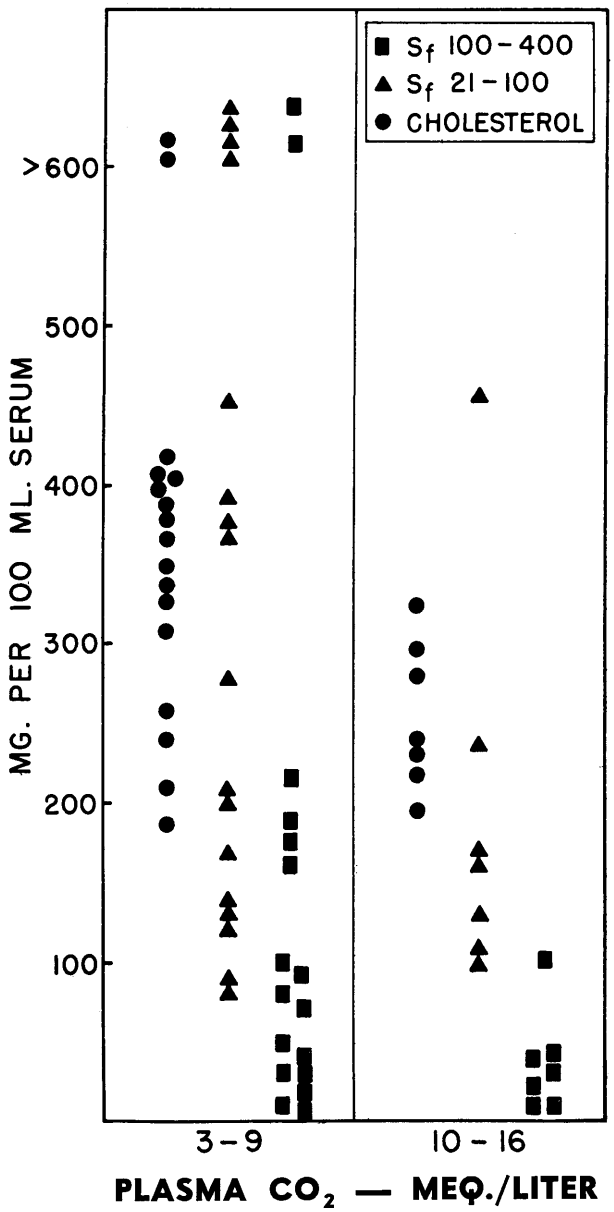


FIGURE 2. The relationship of the initial values of serum total cholesterol and serum lipoproteins to those of plasma CO_2.

done. However, regardless of the role hydration may play in the serum levels of these measured substances, the relative effect on the several lipid components should be the same. Therefore, in any comparison of the relative changes in concentration of one class of lipoprotein with respect to another or to cholesterol, the changes are real and not artefacts due to hydration of the patient during treatment. Allowing for a dilution effect on the measured serum constituents would only intensify the plateaus occasionally seen in the S_f 21-100 band and the plateaus or peaks usually seen in the S_f 12-20 band during this interval of time. With this intensification of the abnormality in level of the various fractions, the comparison of one lipoprotein band concentration with that of another would become more dramatic rather than less so.

A second question arises as to the effect of hydration of the patient on the shifts in concentration found in

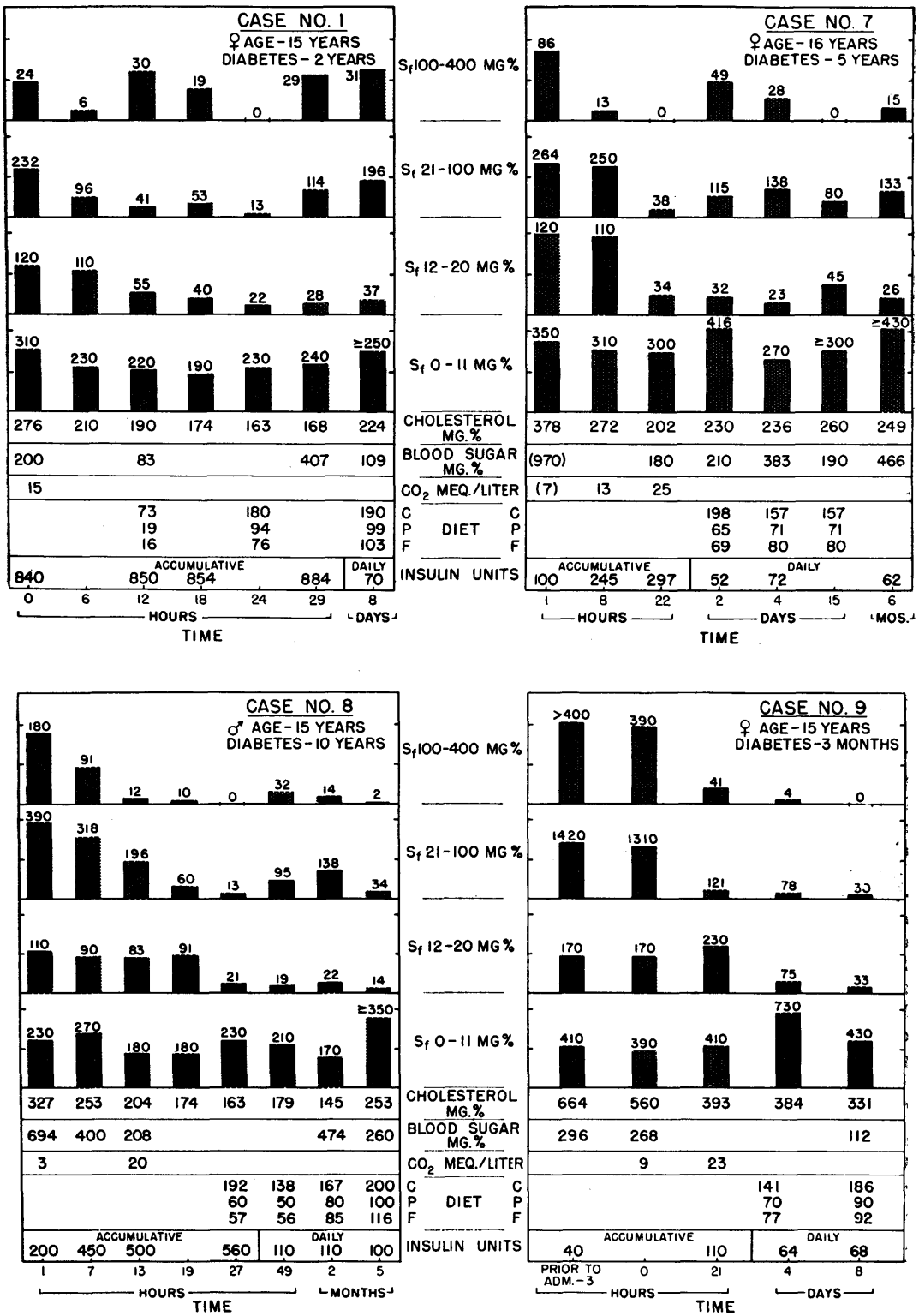


FIGURE 3. Charts of representative subjects showing lipoprotein changes during and after treatment for diabetic acidosis and coma.

any given component. Seldin and Tarail[12] have reported balance studies for patients with diabetic acidosis showing that reconstitution of plasma fluid during hydration would cause a maximum change of 55 per cent and an average change of 33 per cent in the concentration of serum constituents. Hydration would principally effect the percentage change in the first twenty-hour hours of treatment. However, taking into account the most extreme dehydration with a possible 55 per cent elevation of the measured values because of dehydration, the majority of the initial levels of the lipoproteins of the S_f 12-20, 21-100, and 100-400 classes are still higher than those of normal individuals. They are also higher than those of diabetic subjects without vascular complications or with only minimal retinopathy. As shown in the data presented by Keiding and associates[13] diabetic subjects without nephropathy would be expected to show mean levels of 44 and 52 mg. per 100 cc. in the S_f 12-20 and S_f 21-100 bands, respectively. Initial cholesterol values, after taking into account the effects of dehydration, do not show as marked elevation as do the lipoproteins.

More important than comparing a few individuals in this series with statistical summaries of other work is the illustration of the initial lipid defect in individuals by comparing initial values with those after treatment and noting the extent of the fall in concentration. Taking into account an assumed maximal concentration effect due to dehydration, 9 of the 12 patients in coma and 2 of the 6 patients in acidosis showed a drop of more than 55 per cent from the initial values of total cholesterol. In all but two of the cases not showing more than a 55 per cent drop, insulin had been given prior to admission or the first cholesterol values were determined four to six hours after admission; it might be assumed that hydration and a change in cholesterol values had already commenced. It was also observed that there was a drop in concentration from the initial values of more than 55 per cent in the S_f 100-400 lipoprotein band for all patients, in the S_f 21-100 band in all but 2, and in the S_f 12-20 in all but 5 patients. There was only one instance in the S_f 0-11 band in which such a drop in concentration was noted. It should be reemphasized that these changes are all significant despite an assumption of a 55 per cent expansion in plasma volume. If the average figure of 33 per cent is taken, all the lipoprotein classes show a real change in concentration except that of S_f 0-11. Likewise, all but two of the patients would show real changes in cholesterol levels. One of these had had insulin prior to admission, and in the other, the initial determination was made six hours after admission. It is evident from the above discussion that, whether comparisons between the concentrations of different types of lipid measurements are made or whether merely a single component is examined serially during treatment, there is a distinct and obvious lipid metabolism defect in diabetic acidosis which is quickly influenced by therapy. Although cholesterol measurements reflect the defect, the more striking evidence of it lies in the lipoprotein measurements.

A consideration of the sequence of events after treatment of diabetic coma indicated that the various lipoprotein moieties did not subside toward normal levels at equal rates. This is illustrated in Figure 3 (Nos. 1, 8, and 9). The data obtained in case 9 indicate that between the third and twenty-fourth hours of treatment the S_f 20-400 lipoprotein classes were reduced by 90 per cent. In the same interval, the S_f 0-20 classes had increased by 14 per cent. It appears futile to attempt to equate these shifts because of several technical limitations of the procedure, but an attractive explanation for the observation is the proposal of Gofman and associates[10,14] that the serum lipoproteins represent a spectrum of aggregates varying in lipid composition. These authors further proposed that the normal transport of lipid substances is accomplished by a progressive shift of material from lower to higher density, that is, from higher to lower S_f classification. This explanation would imply that in diabetic acidosis an interruption of this orderly transfer has occurred with a resultant accumulation of the low-density material in the serum. This process can be visualized as a wave phenomenon in which diabetic acidosis has acted as a dam. Treatment has broken the dam, releasing material, which has created a measurable ripple all down the lipoprotein channel.

There is some evidence that in certain of these young patients treatment did not completely normalize the lipid transport system, since the S_f 0-11 lipoprotein band and the serum cholesterol did not return to the levels expected in a person of that age and sex. This is illustrated by Figure 1 and patients No. 7 and No. 9 in Figure 3. It is also illustrated by two other patients whose initial values are listed in Table 2 (No. 5 and No. 13) and whose follow-up values after six to twelve months were 480 and 370 mg. per 100 cc., respectively, for the S_f 0-11 band and 431 and 318 mg. per 100 cc., respectively, for cholesterol concentration. In these particular individuals this persistence of abnormal levels may have been related to the presence of diabetic vascular lesions. One patient (No. 13) had diabetic retinopathy prior to this episode of diabetic coma. The other (No. 5) had retinitis proliferans prior to this admission and developed

clinically detectable nephropathy during the year following this coma. As has been pointed out in a previous paper,[13] diabetics with these vascular lesions tend to show high lipoprotein and cholesterol levels. In one case (No. 7) the failure of these lipid values to return to normal may have been due to the poor control reported for the interval of time between discharge from the hospital and the taking of the follow-up sample six months later. In the other two patients, however, the failure of these lipid levels to become normal cannot, at present, be explained.

The charts presented in Figure 3 show examples of the evidence for a return to somewhat higher serum lipid levels. In the second or third day of treatment, that is, within 24-48 hours after significant food intake was commenced, the serum lipoprotein fractions S_f 21-100 and S_f 100-400 increased again. A similar effect in lipid fractions was noted by Harris and associates.[9] An explanation was attempted on the basis that the first minimum was lower than normal for that individual, the norm being taken as the height attained in the four to seven day period following the acidosis episode. However, in our experience, this late increase was transitory in many (10) patients; for example, No. 7 and No. 8 as illustrated in Figure 3. These two patients also emphasize the influence of poor control of diabetes upon the serum lipid measurements. The first follow-up sample of patient No. 7 was taken on the fifteenth day which was obtained ten days following discharge from the hospital. During this interval she was in a diabetic camp, and her disease was under good control. The S_f 21-100 and S_f 100-400 lipoprotein concentrations had dropped from the second peak value observed in the hospital. However, in the intervening six months before the final sample was obtained, the patient admitted to being in poor control, and the concentration of these lipoprotein classes had again risen. In the other patient (No. 8), the two months' follow-up sample was obtained between two other admissions to the hospital in acidosis and coma. The S_f 21-100 and S_f 100-400 concentrations remained elevated. However, in the two months prior to obtaining the final follow-up sample, the patient was, for the first time in a year, in fair control of his diabetes. It should be noted that the concentration of these two classes of lipoprotein was much lower than the transitory peak values and approximated the lowest point reached during the episode of coma and its subsequent treatment.

It was observed that in six cases, the secondary increase in concentration appeared to persist, for example, No. 1; in one or two it was never evidenced (No. 9). These two groups of patients may not exhibit real differences from the major trend of a transitory elevation of lipid concentrations, but may merely indicate that sufficient samples at the appropriate time intervals were not obtained.

Several explanations are at hand for this secondary increase in lipid levels, but none can be substantiated at the present time. It is a well-known fact in clinical circles that the coma patient may show a relapse on the second day, and the rise in lipoproteins could be a consequence of a relative reversion toward acidosis. Perhaps the net insulin deficit has enlarged as insulin doses are reduced and food intake is begun, and lipid values have increased as a result. Or perhaps the secondary lipid rise reflects a kind of lipid tolerance test following the first substantial dietary fat intake after treatment. While these hypotheses may not exhaust the possible explanations, each of them could readily be examined experimentally. However, the present studies do not permit an explanation of the cause of the secondary rise in lipoproteins during treatment of diabetic acidosis and coma.

While the degree of lipid disturbance associated with diabetic acidosis is variable among individuals, we have seen no patient in diabetic acidosis without some increase of serum lipoprotein. Whatever the potential atherogenecity of particular bands or combinations of bands of lipoproteins, the abnormality in diabetic acidosis is both so diffuse and so regular in appearance that this appears to be a reasonable contributing factor in the premature atherosclerosis characteristic of diabetic patients. This is even more important in the light of the studies showing increased lipoprotein levels in diabetic patients with vascular changes.[13, 15] It follows then, that every effort should be made to prevent acidosis as a means of preventing atherosclerosis. In addition, there is every indication from the data herein reported and from those reported by Keiding and others[13] and Barach and Lowy[15] that even generally poor control, which has not reached the stage of actual acidosis, also causes the appearance of abnormalities in the various lipoprotein bands. Thus, it could be inferred that the better the control, the less contribution lipoprotein abnormalities can make to atherosclerosis.

The extent of lipoprotein changes and the rate at which they occur during the treatment of diabetic acidosis is approached in only one other situation; namely, the administration of parenteral heparin.

Thus, diabetic acidosis offers a unique opportunity for the study of the mechanisms that influence lipid metabolism.

SUMMARY

1. Changes in lipid levels were followed during the treatment of diabetic acidosis or coma in 18 patients. Six of these patients were admitted in acidosis and 12 in diabetic coma.

2. Measurements were made of serum total cholesterol and of serum lipoproteins of the S_f 0-11, 12-20, 20-100, and 100-400 classes as well as the routine determinations of blood sugar and carbon dioxide.

3. Diabetic coma is associated with a greater lipid disturbance than diabetic acidosis as indicated by the levels of total cholesterol, S_f 21-100 fraction, and S_f 100-400 fraction of lipoproteins. There is, however, such variability in this relationship that it appears that the basic lipid disturbance is complex and cannot be explained as a simple consequence of the degree of ketosis.

4. Treatment leads to a correction of the lipid substances toward normal levels. There is evidence of a sequential transfer of material through the spectrum of lipoproteins.

5. In the 24- to 48-hour interval following return to substantial food intake the lipoprotein concentrations often increase transitorily.

6. The abnormality of the lipoproteins in diabetic acidosis and the apparent relationship of the degree of control of the diabetes to the premature development of atherosclerosis in diabetic subjects is discussed.

REFERENCES

1 Bloor, W. R.: The lipoids of the blood in diabetes. J. Biol. Chem. *26*:417-30, Sept. 1916.

2 Joslin, E. P., Bloor, W. R., and Gray, H.: The blood lipids in diabetes. J.A.M.A. *69*:375-78, Aug. 4, 1919.

3 Gray, H.: Lipoids in 131 diabetic bloods. Boston M. Surg. J. *178*:16-20, Jan. 1918.

4 Blix, G.: Studies on diabetic lipemia. I, II, and III. Acta Med. Scand. *64*:142-74, 174-233, 234-59, Aug.-Oct. 1926.

5 Joslin, E. P.: Treatment of Diabetes Mellitus. Philadelphia. Lea and Febiger, 4th ed., 1928, p. 243.

6 Man, E. B., and Peters, J. P.: Lipoids of serum in diabetic acidosis. J. Clin. Invest. *13*:237-61, March 1934.

7 Herbert, F. K.: Observations on the blood fats in diabetic lipemia. Biochem. J. *29*:1887-93, July-Dec. 1935.

8 Man, E. B., and Peters, J. P.: Serum lipoids in diabetes. J. Clin. Invest. *14*:579-94, Sept. 1935.

9 Harris, L. V. D., Albrink, M. J., Van Eck, W. F., Man, E. B., and Peters, J. P.: Serum lipids in diabetic acidosis. Metabolism *2*:120-32, March 1953.

10 Gofman, J. W., Jones, H. B., Lindgren, F. T., Lyon, T. P., Elliott, H. A. and Strisower, B.: Blood lipids and human atherosclerosis. Circulation *2*:161-78, Aug. 1950.

11 Abell, L. L., Levy, B. B., Brodie, B. B. and Kendall, F. E.: A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. J. Biol. Chem. *195*:357-66, March 1952.

12 Seldin, D. W., and Tarail, R.: The metabolism of glucose and electrolytes in diabetic acidosis. J. Clin. Invest. *29*:552-65, May 1950.

13 Keiding, N. R., Mann, G. V., Root, H. F., Lawry, E. Y. and Marble, A.: Serum lipoproteins and cholesterol levels in normal subjects and in young patients with diabetes in relation to vascular complications. Diabetes *1*:434-40, Nov.-Dec. 1952.

14 Graham, D. M., Lyon, T. P., Gofman, J. W., Jones, H. B., Yonkley, A., Simonton, J. and White, S.: Blood lipids and human atherosclerosis. II. The influence of heparin upon lipoprotein metabolism. Circulation *4*:666-73, Nov. 1951.

15 Barach, J. H., and Lowy, A. D.: Lipoprotein molecules, cholesterol and atherosclerosis in diabetes mellitus. Diabetes *1*:441-46, Nov.-Dec. 1952.

DISCUSSION

H. C. SHEPARDSON, M. D., (*San Francisco*): Dr. Howard F. Root and his co-workers in the Joslin Clinic have undertaken investigations of the details of lipid metabolism in diabetic subjects. This discussion of the effects of diabetic acidosis and coma upon the serum lipoproteins is a report of one step in this study which began several years ago.

The work of Gofman focused the attention of investigators on the possible importance of various lipoproteins in the development of atherosclerosis. The predilection of diabetic subjects for this complication has been noted for many years. Various morbific factors have been suggested in the past, none of which, however, have satisfactorily explained the premature development of vascular sclerosis in diabetics. It is possible, of course, that the disturbance in metabolism of the large molecular lipoproteins may eventually prove to be the primary inciting disturbance eventuating in the development of clinical atherosclerosis. Certainly there can be no better group of individuals on which study of the lipoprotein metabolism can be carried out than diabetics.

Technical analysis of the results obtained in this experimental work has been satisfactorily accomplished by Dr. Root. In general, however, the results suggest that the severity of diabetes, as measured by the insulin dosage, is far less important as a cause of disturbed lipid metabolism than is the degree of control of the diabetes. Thus, some two years ago Dr. Root reported a higher mean level of serum lipids in diabetic subjects who previously had been poorly controlled, as compared to those subjects who had maintained good control. This present work was carried out on some 18 patients who were either in acidosis or coma—certainly an indication of poor control. Proper treatment of the acidosis lead to a correction of the abnormal level of lipid substances toward normal.

This work would appear, therefore, to suggest strongly that the efforts of the clinician should be directed not only to the prevention of acidosis as a means of preventing atherosclerosis, but also to the maintenance of continuous and rigid control of the disease. Only in such fashion can abnormalities in the various lipoprotein bands be reduced to a minimum—a condition that apparently is essential if the atherogenicity of the lipoproteins is ultimately established. If a continuous state of perfect control is maintained it seems likely that the predilection of diabetic subjects to atherosclerosis will be reduced or even prevented.

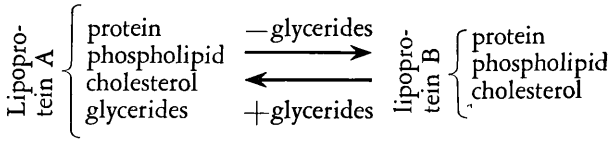
FELIX O. KOLB, M.D., (*San Francisco*): Were there any signs of xanthomatosis in any of your cases?

HOWARD F. ROOT, M.D., (*Boston*): Thank you for that question. None of the patients in this series happened to have xanthoma, but the first patient was a young man of eighteen years who had lipemia retinalis.

Some Aspects of the Chemistry and Biochemistry of Cholesterol

Cholesterol, discovered by Chevreul in 1815 and readily available for experimentation from gallstones or brain, has been the subject of innumerable researches for more than a century, but it still presents certain problems of interest that are under active inquiry. This solid alcohol of the formula $C_{27}H_{45}OH$ is no minor constituent of the animal body. The total quantity of cholesterol in a man weighing 65 kg. is approximately 210 gm., or 0.3 per cent of the wet weight. The largest amounts are present in the skin (51 gm.) and nervous tissue (35 gm.); the tissue concentration varies from 0.14 per cent (muscle) to 4.5 per cent (adrenal gland). The sterol normally present in plasma to the extent of 0.2 per cent is partly free (27 per cent) and partly as esters of higher fatty acids, while that present in red blood cells (0.12 per cent) and in nervous tissue (1.9 per cent) is completely unesterified. The cholesterol of herbivorous animals is derived exclusively by biosynthesis, while that of man is supplied by a combination of biosynthesis and diet. R. P. Cook has demonstrated that the intake of 0.58 gm. of cholesterol per day from an average normal diet can be increased to 6.9 gm. by a regime of menus involving consumption of 20 eggs per day.

What is the role of cholesterol? In what way or ways is it useful to the animal organism? The free cholesterol of nervous tissue appears to serve the function of forming a component of a structural unit of the tissue; Finnean has postulated a specific orientation of the molecules of cholesterol and phospholipid in a complex that, in combination with protein, constitutes the structure of myelin. It seems to me likely that the cholesterol in plasma plays a key role in the transport of neutral fat, by the mechanism suggested in the following idealized representation:



The protein may be the cart, and the lipid part of the sterol may supply a lining for reception of the cargo of other liquid. A possible function of the free cholesterol present in high concentration in the membrane of the red blood cell is to form complexes with, and so detoxify, substances that otherwise would have a hemolytic action. The metabolism of cholesterol is surely associated with that of the steroid sex hormones and cortical hormones, since Block has demonstrated conversion of cholesterol into pregnanediol, a metabolite or progesterone. It is possible that cholesterol serves as precursor both of these hormones and of vitamin D_3.

Is cholesterol, on occasion, also involved in pathological changes? It is assuredly involved in the formation of gallstones, since these are composed of free cholesterol to the extent of 70 to 80 per cent, and in hypercholesteremia, which may be attended with a three- or four-fold increase in blood level. It is involved also in arteriosclerosis, since the sterol content of arteriosclerotic aorta is 5 to 50 times that of normal aorta, but the question of whether or not cholesterol is a causative agent is still uncertain. Myxedema, a disease due to hypofunction of the thyroid gland, is characterized by lowered rate of basal metabolism and augmentation in blood cholesterol. There are some suggestions of an involvement of a spleen sterol in thrombocytopenic purpura but the evidence is very tenuous. There is also the possible carcinogenicity of cholesterol, or of some related or derived substance.

From "Some Aspects of the Chemistry and Biochemistry of Cholesterol," by Louis F. Fieser, in *Science*, May 21, 1954.