tion of our young medical men and women in the process of student training, when a doctor of medicine steps forth into the great neurotic world to gain a livelihood he should be fully conscious of the fact that he is going to be taken seriously by some of his patients, and in order to serve the best traditions of his profession he should be careful to study ways and means by which these patients shall be made stronger physically and mentally, more rugged in mind and body for their adaptation to the great struggle of life. It is his individual duty to help to make the laity strong, and to fight the natural tendency of the laity to make our profession weak. Let this attitude of mind be regarded as a part of our therapeutics, for in it lies the one distant hope of stemming the tide of quackery, that has latterly crept into the healing art, as well as into the fine arts, literature, politics, and even religion.

For the closing lines of this necessarily brief and incomplete analysis of a very important subject, one may recall the words of a poet, even as for the introductory portion,

"Thy word is a lamp unto my feet and light unto my path."

THE CHOLESTEROL CONTENT OF THE BLOOD PLASMA AS AN INDEX OF PROGRESS IN INSULIN-TREATED DIABETICS*

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THE clinical picture, urinary sugar and blood sugar are usually depended upon in estimating the progress of the diabetic. The value which may be attached to any one or a combination of any of these depends upon whether the patient does or does not require insulin.

For the diabetic not requiring insulin, the clinical picture, that is, the attitude, expression, colour and nutrition, when combined with urinalysis, is, on the whole, a fairly reliable guide. In the majority of cases, if the urines are free of sugar, it may reasonably be assumed that the blood sugar is within, or near, the normal limits of variation or at least below 0.18 per cent. The absence of sugar in urine, however, ceases to be an index of progress in those cases in which the normal threshold level of the blood sugar is raised; that is, when sugar is not excreted in the urine at the time the concentration of sugar in the blood reaches about 0.18 per cent. This may occur when the diabetes is complicated by the following conditions: (a) gross dietary indiscretions, (b) arterio-sclerosis, (c) nephritis, (d) infections, and (e) when the diabetes is of long duration. *Under these conditions a knowledge of the blood sugar is indispensable.*

For the diabetic requiring insulin, the clinical picture is not as reliable a guide as for the non-insulin cases. As a matter of fact, it may be very misleading. The temptation to take more insulin and more food than has been prescribed is particularly great. This practice, if uncontrolled, leads to a high renal threshold for sugar. Such patients may, even in the absence of nephritis, arterio-sclerosis, etc., have blood sugars ranging from 0.2 to 0.4 per cent and at the same time have no sugar in the urines. In spite of this, such patients may feel and clinically appear very well. How well they may actually be, as far as pancreatic function is concerned, may be seen from the following case.

Miss K. B., (Hosp. No. 5582-26) twenty-six years old, was referred to our clinic by Dr. J. H. Laidlaw of Ottawa. The diabetes was discovered in 1920, and since 1923 she had been taking insulin. She has found it necessary to gradually increase the amounts, and is now taking 57 units a day. In spite of this the urines frequently show sugar. Dr. Laidlaw noted a high kidney threshold on three occasions, the fasting blood sugars ranging then between 0.4

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and 0.46 per cent. There was a history of frequent dietary indiscretions.

On admission to the hospital, the patient appeared to be very well nourished and had a healthy colour. She felt well and her only reason for coming to the hospital was to adjust the insulin dosage. *The blood sugar was 0.454 per cent and the urine was free of sugar* and acetone bodies.

The following morning she felt slightly nauseated and attributed this to some article of diet or a pill she had received the day before. At this time no sugar nor acetone bodies were found in the urine. In view of the nausea she took no food. This was taken advantage of, and no insulin was given on this day in order to determine, if possible, the renal threshold. The urines were observed at frequent intervals throughout the day, and there was no glycosuria. During the night the nausea became more marked and she vomited twice. At 8 a.m. the following morning she was practically in coma. The blood sugar then was 0.540 per cent and both sugar and acetone bodies were found in the urine. With insulin she recovered and is now well.

What had actually produced the nausea at first is rather difficult to determine. Undoubtedly the discontinuance of the insulin assisted in bringing on coma. The important point, however, is that we have here a patient appearing to be and feeling very well, taking more food than has been prescribed and more insulin in an attempt to balance this excess. Because of this the blood sugar is very high but this is not shown by the urine. With this practice of "more insulin and more food" not only had her tolerance for carbohydrates not increased under the use of insulin, but because of abusing it, the pancreatic function was destroyed to such an extent, that in the absence of it *for one day* only, she was brought to the stage of coma. It is obvious that under these conditions both the clinical picture and the urinalysis are unreliable and a knowledge of the blood sugar is indispensable.

It would appear from the foregoing observations that the blood sugar is the best index of all three measures. Unfortunately, it also fails at times. Diabetics may, though infrequently, in spite of having normal blood sugars, develop carbuncles, neuritis and even gangrene. Have we therefore any other index of progress?

In 1917, Joslin, Bloor and Gray[1] recorded their observations on the blood lipoids in diabetes. These authors by correlating their laboratory data with the various clinical types of diabetes, showed that "all types of diabetes are distinguished by a marked increase in the lipoids of the blood, and the general statement can be made that the increase is progressive with the seriousness of the disease." A rather important observation was that there was no parallelism between the blood sugars and lipoid fluctuations, and that the blood sugar was not nearly as accurate a test of the severity of the disease as was the blood lipoids. In a more detailed study one of the workers of this group[2] again demonstrated a relationship between the lipoid content of the blood and prognosis. "The longer the duration of the disease before examination the lower the blood fat, presumably because those patients live long who have low fats, that is, mild diabetics." In his recent monograph Joslin[3] briefly summarizes our present knowledge of the physiology of blood lipoids, and in a very striking manner further illustrates the prognostic value of their determination. In a survey of the more recent literature on clinical studies of diabetes, one finds that references to blood lipoids are remarkably conspicuous by their absence. An explanation of this is rather difficult in view of the above observations, the technical simplicity with which the test can be carried out, and the small amounts of blood required.

In our clinic we have confined our studies to the cholesterol fraction of the lipoids, and have preferred plasma to whole blood for several reasons. Firstly, cholesterol is a relatively stable chemical compound. Secondly, cholesterol values have been found to run parallel with the total fatty acids, and lastly it has been demonstrated that the plasma affords the best index of changes in the lipoids of the blood. As in the case of blood sugar estimation, all observations were made on blood obtained in the fasting state. The technique described by Bloor[5] is very simple and is as follows:

Preparation of the sample.—Three c.c. of plasma are run slowly (a slow stream of drops) from a pipette into about 75 c.c. of a mixture of re-distilled alcohol and ether (3 parts alcohol 1 part ether) in a 100 c.c. graduated flask. The contents of the flask should be kept in motion during the process so that there is no clumping

of the precipitated material. The contents of the flask are raised to boiling by immersion in a water bath (with constant shaking to avoid superheating), cooled to room temperature, filled to the mark with alcohol ether, mixed and filtered. The filtered liquid if placed in a tightly stoppered bottle in the dark will keep unchanged for a considerable time so that if it is not convenient to complete the determination at once, the sample may be carried to the above stage and left till a more suitable time.

By running the blood slowly into the large quantity of alcohol-ether as above, the protein material is precipitated in finely divided form and under these conditions the short heating combined with the great excess of solvent is adequate for complete extraction of the serum of the plasma. The extraction, while not so complete in the case of whole blood, is believed to be better (because of the higher values obtained) than that obtained by any other method in use at the present time.

Determination.—Ten c.c. of the alcohol-ether extract are measured into a small flat-bottomed beaker and evaporated *just to* dryness on a water bath or electric stove. Any heating after dryness is reached produces a brownish colour which passes into the chloroform and renders the subsequent determination difficult or impossible. The cholesterol is extracted* from the dry residue by boiling out three or four times with successive small portions of chloroform, and decanting into a 10 c.c. glass-stoppered, graduated cylinder which has previously been calibrated. The combined extracts after cooling (5 c.c. or less) are then made up to 5 c.c. The solution should be colourless but not necessarily clear, since the slight turbidity clears up on adding the reagents. Five c.c. of a standard cholesterol solution in chloroform† (containing 0.5 mg. of cholesterol) are measured into a similar 10 c.c. cylinder.

To each of the solutions are added 2 c.c. of acetic anhydride and 0.1 c.c. of concentrated sulphuric acid, the solutions mixed by inverting several times, then set away in the dark for fifteen minutes, after which they are transferred to the cups of the colorimeter (Dubosecq) and compared as usual, setting the standard at 15 mm. The cement of the colorimeter cups must, of course, not be soluble in chloroform; plaster of Paris has been found satisfactory, or even ordinary glue if the cups are not used for any other purpose. In using the colorimeter in this determination the window screen described by Folin and Denis has been found valuable. The error of the above method when carried out with ordinary care is 4 to 5 per cent. If greater accuracy is desired it may be obtained, at the expense of more material and time, by using 50 c.c. of the alcohol-ether extract, evaporating as above, extracting with larger quantities of chloroform, making the extracts to 25 c.c. and taking an aliquot of 5 c.c. for determination.

As a result of our studies we are entirely in agreement with the Boston workers that the lipoid content of the blood is a better index of the course of the disease than the blood sugar, Patients may on discharge from the hospital have normal blood sugars and urines free of sugar. In many of these cases the cholesterol content of the blood is increased. Observing these patients as they return to the Out-Door Clinic, differences in progress are noted. The patient, though with a normal blood sugar, but with high cholesterol, does not, on the average, appear to run the same uneventful course for the same length of time as the patient who not only has a normal blood sugar but also a normal cholesterol. With high cholesterols, the slightest dietary indiscretions result in more marked and more persistent hyperglycæmias than with normal cholesterols. Hyperglycæmias resulting from slight illnesses, appear also to be more frequent with high than with normal cholesterols, and with the former the incidence of neuritis and of vascular changes is greater. (Though neuritis and even gangrene may be observed in individuals with normal cholesterols the number of such cases is not sufficiently great to affect the rule). The relationship between high blood cholesterols and gangrene is striking. In the following discussion we are particularly concerned with the cholesterol findings in insulin-treated patients.

It is generally recognized that, as stated above, a diabetic receiving insulin, though having a

* In order to get an adequate extraction with the small amounts of chloroform used, an excess (3 or 4 c.c.) should be added each time and the mixture allowed to boil down to half its volume or less, before decanting.

† It is convenient to make the cholesterol standard in two strengths: (a) the stock solution containing 0.2 gm. of cholesterol (Kahlbaum) in 200 c.c. chloroform; and (b) the standard solution for use made by diluting 10 c.c. of the above to 100 c.c. with chloroform. 5 c.c. of this latter solution will contain 0.5 mg.

marked hyperglycæmia and glycosuria may feel and clinically appear to be, very well. It seems that, because of this, some workers in this field have actually gone on record as minimizing the significance of traces of sugar in urine, and also discounting mild degrees of hyperglycæmia. It is rather difficult, in view of our conception of diabetes, to be in accord with this view. We have sought, however, to test this idea by cholesterol studies. In drawing conclusions, we are assuming that an increased blood cholesterol is not compatible with favourable progress, that is, *improvement in pancreatic function.*

Method of investigation.—Observations were made upon 254 individuals, ninety-one of which required insulin. Both insulin and non-insulin patients were grouped according to the blood and urinary sugar findings: Thus Group (a) blood sugar normal in the fasting state. Group (b) blood sugar below 0.18 per cent in the fasting state. Group (c) blood sugar above 0.18 per cent in the fasting state: glycosuria. Group (d) blood sugar above 0.18 per cent in the fasting state: no glycosuria.

In each group the maximum, minimum and average cholesterol percentages were calculated. The incidence of normal values was also calculated in each group. The combined data are recorded in the accompanying table.

Since the blood sugar is not necessarily an index of the severity of the disease and since its variations do not always parallel those of the blood lipoids, an explanation of the above method of grouping is necessary. Firstly, the cases have been classified according to severity, otherwise some of these would not be receiving insulin. The classification was that generally employed in this clinic.[5] Secondly in this study we are chiefly concerned with *progress.* Of the three methods usually used in estimating progress, the clinical picture, urinary sugar, and blood sugar, the latter is the most reliable.

Discussion of results.—It will be noted that when the blood sugar was normal in the fasting state, the average cholesterol percentage was normal, and approximately the same in the insulin and non-insulin group. The percentage incidence of normal values tended to be less in the patients requiring insulin.

With patients having mild degrees of hyperglycæmia in the fasting state, some differences were noted between the insulin and non-insulin patients. In the insulin group the average cholesterol percentage was above the accepted normal (0.23 per cent) and the maximum value was also higher. The incidence of normal values was less than in the group of patients with normal blood sugars and definitely lower in the insulin than in the non-insulin group.

With marked degrees of hyperglycæmia, *i.e.* blood sugars beyond 0.18 per cent in the fasting state, all the maximum percentages were

CHOLESTEROL PERCENTAGES IN INSULIN AND NON-INSULIN TREATED DIABETICS

Group	*Normal blood sugar*		*Blood sugar less than 0.180%*		*Blood sugar greater than 0.180% Glycosuria*		*Blood sugar greater than 0.180% No glycosuria*	
	No insulin	*Insulin*	*No insulin*	*Insulin*	*No insulin*	*Insulin*	*No insulin*	*Insulin*
Number of cases	82	18	40	39	27	16	14	18
Maximum percentage of cholesterol	0.317	0.284	0.432	0.516	0.573	0.611	0.564	0.500
Minimum percentage of cholesterol	0.158	0.186	0.182	0.167	0.178	0.197	0.219	0.178
Average percentage of cholesterol	0.205	0.208	0.230	0.258	0.262	0.317	0.354	0.307
Normal values:								
Number	54	11	23	9	10	4	4	6
Percent	65.8	61.6	57.5	23.0	37.0	25.0	28.5	27.7

higher than in the above two groups. All the minimum percentages were within the normal limits of variation. A marked decrease in incidence of normal values was noted whether the patient did or did not require insulin, and whether glycosuria was present or absent.

If the cholesterol content of the blood is an index of prognosis (and this has been definitely demonstrated) the conclusions from the above observations are obvious.

Conclusions

1. Hyperglycæmia indicates active diabetes, whether the individual does or does not show sugar in the urine.

2. Insulin-treated patients cannot be said to have improved, as far as their pancreatic function is concerned, unless the blood sugar in the fasting state is normal. The clinical picture fails to be an index of progress in such cases. This was strikingly demonstrated in the case referred to above.

3. The corollary to these conclusions is that to allow patients to take food in excess of their requirements by allowing more insulin is not ideal practice, since the ultimate aim in treatment should be improvement of the pancreatic function and not merely keeping the individual alive.

4. In view of the small quantities of blood required, and the simplicity and rapidity with which the percentage cholesterol can be determined, this test should be a routine procedure in the care of the diabetic.

5. As with all other laboratory procedures, in the interpretation of results, it is necessary to consider other conditions which may result in increased blood cholesterols, *e.g.*, nephrosis, pregnancy, hepatic disorders, especially obstruction of the biliary passages, occasionally arterio-sclerosis and hemiplegia.

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THE TREATMENT OF DIABETES MELLITUS THROUGH OFFICE PRACTICE*

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THE diabetic individual is fundamentally suffering from an impairment of the internal secretion of the pancreas. This altered function may be due to a temporary depression not associated with altered histological change, or may be definitely a sequel to such change. Secondarily, other physiological functions become deranged; the storage of liver and muscle glycogen, the oxidation of glucose by the tissues, the incomplete combustion of fatty acid with the accumulation of ketone bodies in the blood; hyperglycæmia and glycosuria appear.

Since the diagnosis of diabetes mellitus is not a positive one other causes for glycosuria must be excluded before its certainty can be established. In true diabetes there is usually a group of symptoms, the two most noteworthy being thirst and polyuria which are closely associated with glycosuria, and with glycosuria there is always hyperglycæmia. The condition of renal glycosuria, a local increased permeability of the kidney for glucose, is most commonly confused with true diabetes. But here the blood sugar is always within the normal limits, the glycosuria is little influenced by the diet, and the characteristic symptoms of diabetes mellitus are absent. In hyperthyroidism, hyper-adrenemia, and in other conditions where there is hyperstimulation of the sympathetic nervous system resulting

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