Gall Stones and Cholecystitis.—History of colic or jaundice in a small proportion of cases. High incidence in women. Pregnancy and typhoid predisposing and fatness and increasing weight common. Vomiting, nausea, flatulence, distension. Epigastric pain, right subcostal pain, scapular, interscapular, or shoulder pain. Tendency to diarrhoea or diarrhoea sensations. Shiveriness or slight pyrexia in attacks. Aggravation by exertion, jolting, and menstrual periods. Right subcostal tenderness and catch in breath on deep palpation. Referred tenderness over dorsal spines and eleventh right rib behind. Guarding of right upper rectus and impaired entry at right base in attacks with infected gall bladder. *X* rays seldom helpful. Hyperchlorhydria and achylia both more common than in normal subjects.

Chronic Appendicular Dyspepsia.—Too freely diagnosed. History of possible acute attacks. Epigastric pain without such definite food relationship as in ulcer, but sometimes closely simulating ulcer. Pain in epigastrium on pressure over appendix. Tenderness over appendix shadow when visualized with *x* rays. Positive inflation test. High curves and achylia both more frequent than in normal series.

Post-Gastro-enterostomy Dyspepsia.—This may be the result of gastric discomforts associated with an inefficient or too efficient stoma and consequently with feelings of fullness or empty feelings. It may be due to persistence or recurrence of the original ulcer or to the development of a jejunal ulcer, in which case the maximum tenderness may be found over the stoma, is usually to the left of the mid-line, and commonly at a lower point than obtains in gastric ulcer. In jejunal ulcer there is commonly a persistent high acidity. Fractional test meal shows bile in all specimens after most gastro-enterostomies, but with an unsatisfactory loop bile may be absent in many specimens. Another type of post-gastro-enterostomy dyspepsia is due to too rapid filling of the small bowel. The symptoms are usually discomforts around the umbilicus and below the area of gastric sensibility.

Group C.

Symptoms usually vague. Discomfort rather than pain. Fullness and feelings of weight in epigastrium. Flatulence. Aggravation by prominent causal factors and relief by healthier life, holidays, etc. In fatigue dyspepsias loss of appetite common. Physical examination may show too fat or thin a subject, but local examination negative.

Group D.

History or family history of tuberculosis, or debility in some cases. Poor appetite, especially in morning, with active disease. In latent disease fullness and discomfort, often aggravated by food, and tending to be worse at the end of the day. A tendency to remain below normal weight or to lose slightly. General tendency to fatigue easily. Prompt improvement in appetite and disappearance of symptoms on rest in bed and feeding up. The following is a good example of this type of dyspeptic:

A middle-aged lady who was leading a very active and useful life complained of flatulence and discomfort after food which had failed to respond to ordinary measures. Her appetite was fair, but she was afraid to eat because of the discomfort, which at times amounted to actual pain in the epigastrium. Seventeen years previously she had had a cough for a short time, and on one occasion tubercle bacilli were found in the sputum. Since then she had had no cough nor chest symptoms. The gastric investigations were negative. *X*-ray photographs of chest showed increased root-shadows on the right and small opacities at both apices. There was no pyrexia, cough, nor pain in the chest, and there were no physical signs of active lung disease. She was treated by rest, fresh air, and a liberal diet, which she tolerated well as soon as she rested. Six months later she had gained in weight, from 8 st. 2 lb. to 10 st. 7 lb., and had lost all symptoms.

I have seen several similar cases in which no chest trouble had ever been suspected. It is a type of case which is apt to be treated with a belt, diet, or gastric medication, but when once the cause of the debility to which the gastric mechanisms have reacted unfavourably is recognized the treatment becomes obvious, and the results of treatment are good. In the anaemic dyspeptics heartburn, acidity, poor morning appetite, and a tendency to diarrhoea are common. Relief is given by rest, treatment of the anaemia, and hydrochloric acid.

Group E.

Cases in this group vary from the old man who is concerned about the furring of his tongue to the young woman with hysterical vomiting; from the sufferer from simple aerophagy to the poor victim who blames every cause but the true one for his miseries, and weeds out of his dietary one article of diet after another until he is on starvation rations. The introspective, the worried, the overworked, and the indolent are numbered in the group. There is greater aggravation by anxiety and worries than by physical factors. Pain as a rule is not localized, and the whole hand is employed in the demonstrative gesture, or there may be several pains. In aerophagy left subscapular pain is not uncommon. Subjects may be "nervy," hypertonic, and restless, or they may be hypotonic and depressed. Phobias of internal disease are frequently present. There is aggravation by directing interest and treatment towards the stomach. Relief by explanation, encouragement, unearthing sources of worry, discouraging hurry and worry (especially in the neighbourhood of meal times), teaching relaxation, bromides, and sensible life and dietary. Surgery spells ruin.

CONCLUSION.

I have, with intent, entitled my lecture "The investigation of dyspeptics" rather than "The investigation of dyspepsias." In no branch of medicine is it more important to preserve the wide view—to examine the patient as a whole rather than to concentrate upon his viscus. It is extremely difficult to remain balanced if one employs any single method of inquiry to the exclusion of others—if one comes to rely too much on accessory tests, or too much on clinical tests. I do not believe that there is, or ever will be, a place in medicine for such a specialism as gastrology. If the broad classification which I have outlined has a sound basis it would seem that probably less than one-third of all chronic dyspepsias are due to disease of the stomach, and even in many of these the primary factors have been situated elsewhere.

The introduction of chemical and radiographic diagnostic methods has been of inestimable value, but I believe that the chief value of these methods will finally be in the direction of helping us better to interpret symptoms and so to become more skilled at clinical diagnosis.

The works of Cannon and Carlson in America and of Hurst in this country have supplied a basis for gastro-intestinal symptomatology which has made it possible to study dyspeptics scientifically from the clinical point of view; much in the same way the work of Mackenzie and Lewis has enabled us to study cardiac manifestations reasonably and physiologically. Clinical investigation, we may now affirm, is coming back into its own. Although we shall not hastily relinquish new methods, and although we shall certainly improve upon and add to them, we must admit that we are still in the process of learning to assess them at their proper value. In the dyspepsias, as in other diseased states, it is a truism that early and accurate diagnosis is the first essential for adequate treatment. Early diagnosis depends on appreciation of possibilities and causes and on good clinical sense; accurate diagnosis in many of the dyspepsias can only be arrived at with the aid of routine investigations, the nature and scope and relative importance of some of which I have endeavoured to define. In the past we have commonly had to content ourselves with treating symptoms such as pain, flatulence, and "heartburn." Careful investigation nowadays enables us more and more frequently to discover and attack the causes of these symptoms.

FURTHER CLINICAL EXPERIENCE WITH INSULIN

(PANCREATIC EXTRACTS)

IN THE TREATMENT OF DIABETES MELLITUS.

BY

F. G. BANTING, M.D.Tor., W. R. CAMPBELL, M.A., M.D.Tor.,

AND

A. A. FLETCHER, M.B.Tor.

(From the Department of Medicine, the University of Toronto, and Toronto General Hospital.)

IN this article no attempt is made to give a review of the history of the use of various pancreatic preparations in the treatment of diabetes mellitus. A careful survey of the literature published previous to the use of insulin * indicates that all attempts to obtain a potent pancreatic preparation suitable for the continued treatment of this disease have failed. Many investigators have reported temporary success in the treatment of diabetes mellitus with pancreatic preparations. Owing to the lack of adequate dietetic and chemical control in the treatment of these cases it is difficult to determine the exact significance of their results.

Mention, however, should be made of the work of Zuelzer. In 1908 Zuelzer[1] and his associates reported their results in the treatment of six cases of diabetes mellitus with a pancreatic extract obtained by expressing the juice from the pancreas, treating it with alcohol, and evaporating the filtrate to dryness. The residue, which contained the active principle of the pancreas, was redissolved in salt solution or water and given by injection. Following the intravenous injection of this extract in five diabetic patients kept on a fairly constant diet, the excretion of acetone, diacetic acid, and sugar in the urine decreased or entirely disappeared. An improvement in the general condition of all patients treated was observed following the injection. In four cases the excretion of acetone,

* A general statement of the physiological and therapeutic effects of insulin, by Professor J. J. R. Macleod, was published in this JOURNAL, November 4th, 1922, p. 833.

diacetic acid, and sugar in the urine returned to the former level in from one to four days after extract treatment was discontinued. The fifth case, which was complicated by a large carbuncle, was treated by incision of the carbuncle and by the extract. After the wound healed the urine of this patient remained free of sugar and acetone upon dietetic treatment alone. The intravenous injection of the extract in these five cases was accompanied by severe chills, fever, and occasionally vomiting. In 1909 Forschbach,[2] working in Minkowski's clinic, reported his results in the treatment of two cases of diabetes mellitus with the Zuelzer extract, which he obtained from the Schering Company of Berlin. In one case no effect was observed; in the other the administration of the extract, which was accompanied by chills and fever, reduced the excretion of sugar to one-fifth for a period of forty-eight hours. The writer attributes the positive effect obtained in one case to the use of a freshly prepared extract. Owing to its extreme lability and the severe toxic reaction following its administration the extract prepared by Zuelzer did not come into general use in the treatment of diabetes mellitus.

THE TORONTO RESEARCHES.

In March, 1922, a preliminary report[3] was published on the treatment of severe cases of diabetes mellitus with insulin. It was then noted that insulin could bring about certain definite clinical results. The excretion of sugar in the urine decreased and sometimes completely cleared up. Coincident with the decrease in sugar excretion was a lowering in the blood sugar level, and this level could be brought down to normal or even further by careful adjustment of dosage. Ketone bodies usually disappeared from the urine in twenty-four to forty-eight hours. An increase in the respiratory quotient following insulin injection gave evidence of increased carbohydrate utilization. The patients themselves gave abundant testimony of clinical improvement; their feeling of well-being during treatment, along with the improvement in their physical and mental activity, made it appear that the symptoms which are the immediate result of this disease could be relieved by insulin administration. The effects observed in depancreatized animals following the administration of insulin have been confirmed in cases of diabetes mellitus.

Since the preliminary announcement in March, 1922, applications for treatment have been received in considerable numbers. Among these applications were many from patients with severe diabetes who had been under observation for long periods on well-controlled diets, but with a gradual failure of tolerance for carbohydrates. In view of the limited quantities of insulin available, the need of these patients for relief, and the fact that such patients only can furnish satisfactory data for the establishment of our main propositions, it was decided to confine attention to these severe cases, reserving for future study and treatment the less severe ones. Consequently we are not in a position, at the present time, to furnish any data on a very interesting group of patients whose disease is in the early stage, and who may ultimately show very great degrees of functional repair of the pancreas when the latter is allowed a considerable period of relative inactivity as a result of treatment.

A general plan of investigation and treatment of patients has been adapted provisionally to determine those who require treatment with insulin and the requisite dosage to be employed. On admission to hospital the history and physical condition of each patient is investigated. Patients admitted in coma or in the precomatous state, whether of the accidental type occurring with a good tolerance or as a sequel to slowly deteriorating carbohydrate tolerance, are immediately given insulin treatment. For other cases a diet based upon the normal basal calorie requirement for the age, height, weight, and sex of the patient is calculated.* This diet contains sufficient protein to maintain nitrogenous equilibrium and carbohydrates and fats in such a ratio as to avoid the excessive production of acetone and diacetic acid. Placing patients on fasting for a day has helped to attain constancy of sugar excretion more rapidly. Patients are kept in bed for a variable period following admission to hospital, and afterwards only light exercise is permitted. Examinations of the blood and urine are carried out daily for a period of a week or more. At the end of this period on a constant diet the patients who are sugar-free are advised to continue dietetic treatment in view of the shortage of insulin. Those who are showing decided glycosuria and hyperglycaemia, with possibly various degrees of acidosis in addition, are selected for insulin treatment.

Having a preparation of insulin known to be potent and to contain approximately one unit to one cubic centimetre according to the pharmacological assay,[4] the patient is given an amount calculated to be somewhat less than that required to render the urine sugar-free. If, however, we have an accurate idea of the sugar-burning power of this preparation by previous use in other patients, we may at once calculate the dose required to render the urine sugar-free for the twenty-four hours. Insulin is administered, according to the amount required, in one, two, or three doses, at or shortly before meals. Subcutaneous injection is the method of choice. Examination of the urine at short intervals enables one to determine approximately when the patient becomes sugar-free, and to adjust subsequent dosage to maintain this condition. Blood sugar estimations are useful in determining the level of blood sugar during treatment, and assist in spacing the time of administration of extract.

Special care is taken that the food consumed by each patient is appetizing in appearance, palatable to the taste, and well served. It is all weighed and checked according to a menu prepared by the dietitian attached to the clinic. Any unused food is weighed and the amount actually used determined. Records are kept of each article of food eaten by the patient, and in many instances this is kept constant for long periods as to amount, kind, and time of serving. Atwater's tables are used as a basis of calculation, together with certain later data available in the recent literature and from our own laboratories. Actual analyses of foods consumed are not made except for special purposes, but it is well known that, considering the other factors involved before assimilation of the foodstuffs, the calculation of the diet from published analyses is sufficiently accurate. Non-nutrient materials, such as bran cakes, agar jellies, thrice-boiled vegetables, mineral oil mayonnaise, broths, tea, coffee, etc., are made use of extensively to provide bulk and increase the palatability of the diet.

Twenty-four-hour specimens of urine are collected in the usual manner, and examined qualitatively and quantitatively for sugar, acetone, diacetic acid, and total nitrogen, as well as the usual routine tests for volume, specific gravity, albumin, and character of the sediment. Sugar is determined by Benedict's and Shaffer and Hartmann's methods; ketones (acetone and diacetic acid) by Rothera's and Gerhardt's tests and Van Slyke's methods. Total nitrogen is determined by a modification of the well-known Kjeldahl method. Blood sugar is estimated by the revised Folin Wu and Shaffer-Hartmann methods; blood ketones by Van Slyke's methods; carbon dioxide combining power of the blood by Van Slyke's method; alveolar air carbon dioxide by Marriott's method and a modification of Haldane's method, similar to Roth's. Basal metabolism and respiratory quotients are determined by the Douglas Haldane and Tissot-Haldane methods. Many of these chemical methods are not necessary for the actual clinical treatment of a diabetic patient but are useful for a metabolic study of the disease.

GENERAL CLINICAL RESULTS.

Up to the present time over fifty cases of diabetes mellitus have been treated with insulin, and some have been under treatment continuously for several months. Although the most striking results have been seen in children and young adults, all patients have been benefited by the treatment. Many of the patients have come to the hospital in a state of extreme under-nutrition, suffering from great weakness along with an indisposition to any physical activity. On the first or second day of treatment, if sufficient insulin is given, the urine becomes sugar-free, and on the second or third day ketone-free. These patients become conscious of increasing strength before the end of the first week. From a state which may be one of discouragement or of profound mental depression they become cheerful and interested. Hunger is replaced by appetite; the thirst is lessened oedema, which is common in these cases, disappears. Patients find they are less irritable, and state that they begin to sleep well. The expression improves; the skin becomes less harsh and dry; even the hair becomes softer; in fact, the patient loses that appearance which characterizes the diabetic. In ten days a very considerable amount of physical vigour is restored. Some patients have been able to return to work after a month of treatment. The patient's weight frequently increases, and this can readily be brought about by supplying food in excess of the calorie requirement and increased amounts of insulin.

*Full details as to the calculation of diets will be published shortly by one of us (W. R. C.).

One patient, aged 16, who had lost 40 lb. during her three years of diabetes, gained 35 lb. in less than four months. Mild infections are favourably influenced; for example, the pain of a chronic pyorrhoea was relieved by treatment; it recurred when the injections were stopped, and was relieved again when they were continued. Simple catarrhal infections are no longer of serious import. During this time the urine can be kept sugar-free and ketone-free. The morning blood sugars are lower and may approach the normal level. Lipaemia was present in a few cases and disappeared with treatment.

The following case is reported briefly:

T. H. B., aged 25; glycosuria discovered November, 1920, when the patient was suffering from a series of boils. Weight at that time 160 lb. Has been under continuous dietetic supervision since onset. Glycosuria became much worse in November, 1921, when increase in diet was tried. Condition became progressively worse up to time of admission, September 18th, 1922. During ten days of preliminary observation his weight varied between 112½ and 116 lb. He was emaciated, weak, and depressed. He was given a diet of protein 36 grams, fat 140 grams, carbohydrate 41 grams. Average daily excretion of urine 4 litres; specific gravity 10.10 to 10.16; glucose 38 to 75 grams; ketones, varying from 0.3 to 1.7 grams; total nitrogen 8.5 to 12 grams; morning blood sugar 0.215 per cent. For two weeks following October 4th he was given three daily injections at meal time of 2 c.cm. of insulin. After the first day he remained sugar and ketone free. Urinary nitrogen was on the average 1.5 grams less than before treatment. Fasting blood sugar on the fourteenth day was 0.134 per cent. The restoration of strength was rapid and by the end of two weeks the patient was able to take daily walks of two and three miles. On October 26th he was discharged, and continued to receive 3 c.cm. of insulin a day His diet was increased to—protein 36 grams, fat 140 grams, carbohydrate 61 grams. He is feeling well and strong. He states that he does his work as a bank clerk with ease, and is quite free from fatigue at the end of the day. He has remained sugar-free since discharge. On December 5th the examination of a twenty-four-hour specimen of urine gave—volume 2,880 c.cm., specific gravity 10.08, sugar absent, acetone absent. His weight was 125 lb.

GLYCOSURIA.

Probably the condition toward the alleviation of which most attention has been directed in the therapy of diabetes is the glycosuria. While regarding this symptom as being, in most cases, of not more than secondary importance, it is nevertheless one in which the efficiency of insulin may be most convincingly demonstrated.

We have encountered no cases of diabetes mellitus in which insulin, given in adequate amounts, did not make patients aglycosuric within a remarkably short time, in spite of the fact that they had been excreting large quantities of sugar for months while on a fixed diet, and even in spite of large increases (1,000 calories) in the various foodstuffs. Maintenance of a patient without glycosuria may be a more difficult proposition, and involves a good many factors which will be touched upon later. However, in conjunction with a reasonably well controlled diet on which, without insulin, the patient formerly excreted large quantities of sugar, this has been accomplished for long periods. The dosage of insulin required to effect this has naturally varied in different cases and with various preparations of the pancreatic extract, but as a rule is much less than is required initially to render the patient sugar-free. Certain cases indeed may, after a period of insulin treatment, recover such a degree of tolerance as no longer to require extract to maintain them on a basal diet. The treatment and final outcome of such patients is a most interesting subject for future investigation to determine. We are at present inclined to the opinion that the newly regained tolerance of these patients should be protected for a time by the use of small amounts of insulin. An illustration of some of these points occurs in the case of a man aged 57, who entered the hospital on November 10th, 1922. He was placed on a diet of protein 27 grams, fat 116 grams, and carbohydrate 34 grams, and containing 1,288 calories. He remained on this diet for nine days, during the last four of which the sugar excretion was 27 grams a day. On November 19th the diet was increased for certain reasons to 2,280 calories, and was composed of protein 60 grams, fat 200 grams, and carbohydrate 60 grams. Simultaneously the dose of a certain batch of insulin required to make him sugar-free on the increased diet was calculated and administered on the same day. The result was that the patient has been sugar-free continuously since that time on the same diet, though the dosage has gradually been reduced to half the original amount.

KETONURIA, ACIDOSIS, AND COMA.

In practically all patients accepted for treatment an additional problem has presented itself in the management of varying degrees of disturbed fat metabolism—ketonuria, acidosis, and coma. Ketonuria, associated with glycosuria, clears up when sufficient carbohydrate is burned, and this result can sometimes be brought about by dietetic treatment alone. Under insulin treatment ketonuria is relieved in a striking manner, as in the following case: This patient, who on the previous day excreted 27.3 grams of sugar and 6.70 grams of ketones, was given one dose of 4 c.cm. of a certain preparation of insulin at 7 a.m. The urine was free of sugar at the end of two hours and of ketones in four hours. Sugar was again found in the urine at ten hours after the injection, ketones in eight hours. It is of interest to note here that ketones reappear in the urine two hours before sugar.

TABLE I. — *Showing the Two-hourly Output of Sugar and Ketones in the Urine for the Twelve-hour Period following the Injection.*

Time.	Volume, c.cm.	Sugar.		Ketones.	
		Per cent.	Grams.	Mg. per litre.	Mg. per 2 hrs.
7—9	40	0.75	0.3	1737	70
9—11	250	0	0	262	66
11—1	520	0	0	0	0
1—3	460	0	0	0	0
3—5	470	0	0	213	100
5—7	240	0.43	1.16	491	115

Cases of severe acidosis show the same prompt reaction to insulin treatment. Ketones disappear from the urine and blood, the normal alkali reserve of the blood is re-established, and the signs and subjective symptoms of the condition completely disappear.

To those who have previously striven, practically unrewarded, with cases of diabetic coma, one of the most interesting and valuable properties of insulin is its effect upon this condition, the mechanism of which we believe will throw an entirely new light on the intermediary metabolism of the foodstuffs. We have had an opportunity of treating 10 cases of complete coma (stage of complete anaesthesia) as well as other cases of coma imminens.

Of the 10 cases of complete coma treated 4 died. The first case of coma was admitted to hospital in February, 1922, and died in April. This case came into the hospital in a state of severe acidosis, markedly emaciated and dehydrated, with a high D/N ratio. Owing to the difficulty in the production of insulin at that time many of the preparations lacked potency and satisfactory treatment was impossible. The patient was treated at intervals with insulin. The acidosis was improved, to return when treatment was discontinued. The case gradually became worse and went into coma; was brought out by large doses of a weak extract; lapsed again into unconsciousness and died when the supply of extract was exhausted. One other fatal case was effectually brought out of coma but died of pneumonia. In the other two cases, one died with sloughing gangrene of the foot, and the other of complete vasomotor failure. In both these cases coma was relieved by insulin treatment. At the time of death the urine of these patients was free of sugar and ketones; the blood sugar and blood ketones were normal, and glycogen was found in the liver and muscles *post mortem*.

The remaining six cases of coma treated are all living. One has recovered and is now aglycosuric without insulin on a diet about double the basal requirement. The other five patients have remained free of symptoms and the urine free of sugar and ketones under dietetic treatment and the daily administration of insulin.

We are not prepared, at present, to lay down definite rules for the management of diabetics in coma, for we believe that with greater opportunities for study more satisfactory methods may be devised for treating this as well as other problems in relation to the disease. The use of large amounts of fluids by mouth, by the rectum, interstitially, or intravenously, seems very desirable. Rest, warmth, purgation, and stimulation in suitable amounts seem indicated. Sodium carbonate or bicarbonate presents difficulties in arranging proper dosage and undoubtedly kills when used in excess. There is some evidence of the usefulness of the intravenous injection of glucose as a diuretic in the earlier stages of coma. The fact remains, however, that in the past four years no case entering our wards in advanced diabetic coma has recovered by any of these methods. Though we are aware of a few isolated instances of such having taken place in other hospitals, we

believe the opinion is commonly held that such cases are practically hopeless. Insulin treatment may now be said to constitute an important step in the therapy of this condition. Insulin is administered to these patients either subcutaneously, or intravenously followed by subcutaneous injections. The dose employed has been usually, though not always, far in excess of the requirement, and the danger of a hypoglycaemic reaction is guarded against by sufficient glucose given at the same time. No attention need be paid to the glycosuria at this time, as the object is to correct the disordered fat metabolism and decrease ketone production. The glucose is necessarily given intravenously in advanced coma, and perhaps it is not amiss to warn against the danger of using any but the purest form of glucose and against sterilization at unnecessarily high pressures.

The first evidence of improvement is in the rise of alveolar CO_2, but the difficulties of getting satisfactory samples of alveolar air from comatose patients leave something to be desired in the way of constancy of results, and so clinical improvement usually is noted first, and consists in movements, fluttering of eyelids, etc., response to painful stimuli, etc. At the same time, however, there is reduction of the total ketones in the blood, though this information is usually received too late to be of service. The alkali reserve, as estimated by Van Slyke's technique, is more rapidly determined, and may be used to confirm the clinical impression. It tends to rise toward normal a little later, in our experience, than the reduction in blood ketone bodies, and distinctly later than pronounced clinical signs of improvement.

Probably a considerable number of us have been formerly misled by clinical evidence of apparent improvement in the patient which was not confirmed by laboratory data, and which we subsequently found to be unreliable. But, as well as strengthening our position from a clinical standpoint, the laboratory data also provide definite indications as to the necessity of administering further amounts of insulin or glucose. In the presence of a decided lowering of blood sugar the latter is desirable; while inadequacy of insulin dosage is indicated by failure of the alkali reserve to increase. When laboratory facilities are unavailable, a great deal of valuable information may be obtained by frequent examinations of the urine. Disappearance of sugar from the urine is an indication for the administration of more glucose or possibly the use of epinephrin; while reduction or disappearance of the ketones is a most favourable sign.

Reactions and Hypoglycaemia.

Toxic reactions may follow the injection of an extract of any animal tissue, owing to its content of protein and split protein products. These reactions have been especially severe in the experience of investigators with pancreatic extracts, and have been the chief obstacle to their introduction for clinical use. Some reactions of this type were produced by injections of the extract first used by us. The present product, however, is practically protein-free, so that, with the exception of urticarial eruptions in one, or possibly two, sensitive patients, these occurrences are no longer met with. Insulin administration may be followed by a reaction of another kind, which is the result of the fall in blood sugar (hypoglycaemia). When a single injection is given to a patient there is a rapid fall of blood sugar which reaches a low point in two to eight hours, and tends to return to the original level in twelve to twenty-four. Such a result is recorded in Table II.

TABLE II.—*Showing the Fall in Blood Sugar following a Single Subcutaneous Injection of Insulin, given at 7 a.m.*

(The urine was free of sugar from 9 a.m. to 3 p.m.)

Time.	Blood sugar percentage.
7 a.m.	0.278
9.30 ,,	0.174
11 ,,	0.105
12.30 p.m.	0.073
3 ,,	0.127
6 ,,	0.168

While the extent of this fall is dependent in a measure upon the amount of insulin and upon the initial blood sugar level, it cannot be predicted with any great degree of accuracy in an individual patient. In giving a dose, therefore, to render the patient sugar-free it sometimes happens that the blood sugar falls well below the normal level, and this sudden hypoglycaemia is accompanied by a characteristic train of symptoms. When the blood sugar percentage falls to 0.07 per cent. under the influence of insulin, the patient becomes aware of it. He may first complain of hunger, or more often a sense of weakness or fatigue, and, especially if it is his first reaction, he is conscious of some anxiety or of what he calls nervousness, or he may even show the signs of a definite neurosis with loss of emotional control, such as crying spells. Almost constantly present is a feeling of tremulousness; actual tremor is rarely seen. The patient may also have some inco-ordination for fine movements. Vasomotor phenomena are common: pallor or flushing, sometimes one after the other; a sense of heat or chilliness; almost always a profuse sweat. The severity of these symptoms increases with the hypoglycaemia, and the lowering of the blood sugar near to 0.05 per cent. produces very acute distress or even mental disturbances, such as confusion and disorientation. A blood sugar of 0.032 per cent. resulted in a state of coma with hypotonia and loss of deep reflexes. One patient while asleep passed into a low muttering delirium as the blood sugar fell to 0.052 per cent. This was followed by uncontrollable hunger. A blood sugar of 0.053 per cent. in another case was accompanied by weakness, crying, and extreme anxiety. One patient was quite irrational while his blood sugar was around 0.06 per cent. On another occasion he became deaf and had difficulty in articulation. This difficulty in articulation has been seen several times. Others have had only a vague feeling of uncertainty which would have passed unnoticed had they not experienced a previous reaction. In such cases the blood sugar is usually about 0.075 per cent.

These reactions can be relieved by food administration; 50 to 100 c.cm. of orange juice has an almost immediate effect in clearing up the symptoms. A better result is obtained with 5 to 25 grams of glucose given with orange or lemon juice. When a patient is unconscious 1 c.cm. of epinephrin (1 in 1,000 solution) should be given intramuscularly, followed by glucose by the mouth. If the patient is not well enough in a few minutes to swallow glucose, it may be given subcutaneously or intravenously. Special nursing precautions should be taken for the detection of reactions when insulin treatment is first started, when a new preparation is given, and when insulin is administered late in the day, as the reaction may occur during sleep. As yet pharmacological assay of the potency of insulin has not been satisfactory, and to this may be attributed the occasional reactions seen when new preparations are used. However, once a patient has had a reaction he is quick to recognize the onset of the next one, and means may be taken to relieve it. Up to the present time no serious mishap has occurred as a result of these hypoglycaemic reactions, but while this is so it is felt that hypoglycaemia constitutes a real source of danger.

General Discussion of Results.

The dosage of insulin is a very important factor in the successful treatment of a patient; on the one hand, we have to fear hypoglycaemic reactions, and, on the other, we know that glycosuria will result when the blood sugar rises above the patient's threshold level for excretion of sugar. It is, therefore, not always easy to adjust the conditions so that there is sufficient insulin present to nullify the post-prandial hyperglycaemia, and yet insufficient to produce a dangerous lowering of the blood sugar. We know, however, that the effect of insulin on blood sugar is not exerted immediately after subcutaneous injection, and therefore we space the injections so that their effect is occurring during the period of assimilation of carbohydrates. This usually means injecting the insulin at, or shortly before, the meal, but instances occur—possibly due to delayed, or too rapid, absorption of sugar into the blood stream, the use of meals containing too much high carbohydrate food, etc.—in which glycosuria occurs at one time and reaction at another. These, fortunately, are not common, but serve to emphasize the necessity for careful observation of the patient for a period in a hospital before discharging him to the care of his private physician. Further, the initial symptoms of reaction are so specific as to leave no doubt in the mind of anyone who has seen them, and the remedy is, fortunately, easy to apply before there is any real danger.

At the end of the preliminary period of observation on a fixed diet the majority of cases of severe diabetes excrete a fairly constant amount of sugar, and this information is most valuable in determining the actual amount of insulin to be employed in treatment. In certain cases, possibly owing to daily fluctuation in tolerance for carbohydrates, the daily excretion of sugar varies and it is impossible to determine the initial dose of insulin. In these cases it is advisable to begin with a moderate dose, gradually increasing it until the

desired effect is obtained. The amount of insulin used will depend not only on the carbohydrate tolerance of the patient, but on the height and fixity of the blood sugar level.

Whether we shall in the future permit patients to have higher blood sugar levels than at present seems advisable is a point on which there is conflicting evidence. At present we are inclined to the belief that more successful results are obtained with regard to the general well-being of the patient, clearing up of minor and even major infections, etc., if a normal blood sugar level is aimed at. Owing to the short duration of the effect of insulin it might seem desirable to ingest the carbohydrates at one particular meal and give the extract in relation to this meal, thus avoiding the number of injections—two to three daily sometimes necessary in the severer cases. This, however, is not the case, as the carbohydrate is apparently stored and burned under the influence of the insulin, and during this period the patient feels like a healthy, normal person, and later, when only fat and some protein is available for burning, he gets a mild ketosis and experiences lassitude or fatigue. In our view a prolongation of the period of action is most desirable, and whether this is to be obtained by slowing the rate of absorption or by more frequent injection is a matter for further study.

After these patients are freed from glycosuria and ketosis and are permitted to use an adequate basal ration they usually feel so well that they demand increased food to satisfy their desire for exercise. In this case we are less particular about spreading the carbohydrate intake throughout the day and usually prescribe an increased amount of carbohydrate with three to four times as much fat at one or possibly two meals, and a corresponding amount of insulin. The same thing may be accomplished by raising the diet instead of decreasing the initial dose of insulin. As the protein is not as efficient as carbohydrate in preventing disordered fat metabolism, the amount of fat which can be given with protein is much less than with carbohydrate. Owing to the high caloric value of fat it seems desirable to raise first the carbohydrate in the diet. When increase in calories is not so urgently required, then protein may be used and fat added in the proportion of 10 grams of fat to each 8 grams of additional protein.

In severe diabetics and comatose patients the alterations in metabolism under the influence of insulin are most interesting. They furnish material for a considerable amount of investigation which we hope to report upon later. The study of the respiratory quotient reveals positive evidence of the utilization of carbohydrates. Patients with any considerable carbohydrate tolerance may be expected to produce a certain amount of insulin themselves. This may be mobilized under suitable stimuli, and the initial rise in the respiratory quotient sometimes seen is probably due to this factor. The specific effect following the administration of insulin is almost coincident with the attainment of normal blood sugar levels. Demonstration of the effect of pancreatic extracts in raising the respiratory quotient can best be made on the most severe cases of diabetes mellitus.

Other factors which we must decide in the patient's interests are his most suitable weight and condition of nutrition and the means which shall be employed to attain them, and also to what extent work shall be allowed. Following the principle of low maintenance diets in treatment it seems unwise to allow increases in weight in stout patients, or even marked increases in the emaciated. In the former, reduction of the patient's weight by using insufficient fat in the diet is recommended; in the latter it is felt that some increase in the weight is desirable on account of the associated improvement in the general condition of the patient, his resistance to infection, etc., even though an increased amount of insulin is required. Work, involving as it does the increased use of foods and consequent drain on the supply of insulin, is not to be regarded as desirable when pushed to excess, and patients are accordingly advised to moderate their usual activities.

Diabetics are perhaps more subject to infections and gangrene than any other class of patients. In such cases a distressingly high mortality has been observed. Without doubt the more recent dietetic treatment has removed many of the terrors of operation, such as coma, and has even aided in the more rapid clearing up of infections for the less severe degrees of the disease. However, many patients lose a great deal of their carbohydrate tolerance when infection is added to their diabetic condition. And further, the infections are more prone to occur in the more severe cases who do not respond favourably to dietetic treatment. For both types of patients insulin furnishes most valuable assistance in treatment in that it keeps the blood sugar normal—an important consideration in the treatment of infection—enables the patient to utilize carbohydrates, and, in consequence, prevents acidosis and removes the danger of post-operative coma. It seems clear that necessary surgical procedures may be undertaken in properly treated cases with practically no more risk than in the normal.

Attention must be paid to various other influences in the treatment of diabetic patients. Symptomatic treatment for minor complications, such as constipation, insomnia, etc., must be carried out. Psychic factors, such as fear, anxiety, and worry, are well known to produce hyperglycaemia and glycosuria. The effect of insulin is so specific that these need not be considered as influencing the results of treatment, but in this, as in all other diseases, the best results in treatment can be obtained with happy, contented patients.

SUMMARY.

The following is a summary of the results of our investigation:

1. Under treatment with insulin in patients who are not otherwise amenable to treatment:
   - (*a*) Glycosuria is abolished;
   - (*b*) Ketones disappear from the urine and the blood;
   - (*c*) Blood sugar is markedly reduced and maintained at normal levels;
   - (*d*) The alkali reserve and alveolar carbon dioxide of patients in acidosis and coma return to normal;
   - (*e*) The respiratory quotient shows evidence of increased utilization of carbohydrates;
   - (*f*) The cardinal symptoms of diabetes mellitus are relieved and the patients show well-marked clinical improvement.
2. Insulin is a specific in the treatment of diabetic coma.
3. Certain procedures are suggested as a guide in the administration of insulin.
4. Hypoglycaemic reactions in man have been studied and described.
5. Hypoglycaemic reactions following insulin are relieved by the administration of carbohydrates and also by the injection of epinephrin.

To Dr. Duncan Graham, professor of medicine, we desire to express our sincere thanks for his interest in directing and supervising the investigation throughout its course.

REFERENCES.

[1] Zuelzer, Dohrn and Marxer: *Deut. m d. Woch.*, 1908, vol. 32, p. 1380. [2] Forschbach: Ibid., 1909, vol. 47, p. 2053. [3] Banting, Best, Collip, Campbell, and Fletcher: *Canadian Med. Assoc. Journ.*, March, 1922. [4] Banting, Best, Collip, Macleod, and Noble: *Amer. Journ. Physiol.*, 1922, vol. 42, p. 162.

ON A POSSIBLE MODE OF CAUSATION OF DIABETES MELLITUS.

BY

L. B. WINTER AND W. SMITH.

(From the Biochemical Laboratory, Cambridge.)

IN a paper, now in the press,[1] we show that the normal blood sugar in man and animals has a lower rotatory power than would be given by the α-β equilibrium form of glucose as deduced from the copper reduction value. The sugar gives an osazone with the same crystalline form and melting point as that of glucosazone. The instability of the sugar is shown by its transient rotatory power, the curve of polarimeter readings reaching the copper reduction value in three to four days in acid solution. The sugar at first decolorizes potassium permanganate more rapidly than a solution of α-β glucose in similar concentration. This distinction no longer obtains when the polarimeter reading corresponds with that of α-β glucose. These facts, in conjunction with the work of Hewitt and Pryde[3] on sugar solutions introduced into the intestine, suggest that normal blood sugar is γ glucose. That ingested glucose or fructose is rapidly converted into normal blood sugar was shown by feeding experiments on normal persons. After 100 to 150 grams of glucose or fructose no alteration in the nature of the blood sugar could be detected.

In cases of diabetes mellitus we show that this sugar is not present in amounts capable of detection by the method employed. The polarimeter reading in these cases is initially greater than the copper reduction value, and the