An Address

ON

DIABETES: WITH SPECIAL REFERENCE
TO HIGH CARBOHYDRATE DIETS*

BY

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In 1923 a hundred units of insulin cost twenty-five shillings, and the scanty supplies and excessive price dominated the therapeutic possibilities. It was then customary to continue the previous low-carbohydrate low-calorie diets of the Allen period, and to add the minimum of insulin that would keep the diabetes under control. The idea that the disease might be greatly improved, or even cured, by keeping the blood sugar as continuously normal as possible also contributed to the continuation of pre-insulin diets, a hope which has not materialized.

In 1927, when diabetes was discussed at the British Medical Association meeting at Edinburgh, attention was chiefly focused on the power of insulin to keep severe diabetics in normal health and to rescue them from coma, and no radical changes in dietary were suggested. The openers, MacLean and Petré, were still using very low carbohydrate diets (20-30 grams), and the latter, minimal carbohydrate and protein with very high fat—200 grams or more. A few workers in this country had raised the carbohydrate to from 50 to 100 grams, but seldom higher, and fat still predominated as the calorie producer in the diabetic diet. At this time, therefore, the abundant and cheap supply of insulin, 1s. 6d. to 2s. per 100 units, had not greatly affected the diets used.

Since then considerable changes in diabetic diets have been introduced in the direction of higher and more normal amounts of carbohydrate, and this forms the chief subject of our discussion. Before going into this in detail it may be useful to outline the present position of diabetes and insulin in their more theoretical aspects.

THEORETICAL POSITION OF DIABETES AND INSULIN
TREATMENT

Whatever may be the undoubted advances in practical treatment it must be admitted that fundamental knowledge on the subject has not progressed much. Crystalline insulin, whose activity is 24 units per milligram of weight, has been prepared, but it is not certain that these crystals represent only the active principle. Insulin in this form is a protein molecule containing 3.2 per cent. of sulphur, and is stated to have glutamic acid and cystine as characteristic groupings. A formula has been tentatively suggested, and it may not be long before we actually know what insulin is. Unfortunately, in the meantime, no advance has been made in the administration of insulin by any method other than injection, an advance most urgently needed in diabetic therapy.

Nor, in spite of extensive research by many of the most famous investigators in physiology and biochemistry, has the intimate nature of insulin action become clear. It undoubtedly rectifies not only the disordered sugar but also fat metabolism in diabetes, but the details of these functions are still obscure.

Nor do we know more of the cause and essential nature of diabetes. Indeed, new facts have been observed which introduce new complexities. There is evidence to show that the secretion of insulin is, partially at least, under

the control of nerve impulses transmitted by the vagi, as well as the humoral influence of hyperglycaemia acting direct on the islet cells of the pancreas.

The complicating influence of other endocrine organs on carbohydrate metabolism has been more clearly established. Most novel and important animal experiments by Houssay¹ have redirected attention to the influence of the pituitary gland. When the pituitary body is removed, subsequent pancreatectomy does not produce the classical severe and fatal diabetes in animals, but this severity is re-established by injections of anterior pituitary extracts. On the clinical side Cushing² has described a new type of pituitary disturbance producing diabetes ("pituitary basophilism"), and the amelioration of the pituitary syndrome by x-ray therapy has led to the complete disappearance of the associated diabetes. It seems probable that pancreatic (insular) failure is present in such cases, secondary to the other endocrine disturbance. At any rate, insulin rectifies this carbohydrate disturbance, as it does all forms in my experience, whether primarily produced by the more common acromegalic upset of the pituitary or the thyroid or possibly hepatic diabetes. The total regulation of blood sugar is certainly the most important nutritional factor in our bodies, and we need not be surprised that it is intricately dependent on many complex endocrine factors.

Whatever the theoretical problems, the practical fact remains that insulin works, and works extraordinarily well. When properly used it restores normal health and activity to the severest diabetic if no complications are present. It has assured the normal development of thousands of children, and made severe operations safe for all diabetics.

But it must be admitted that this is not the happy state of every diabetic in this or any other civilized country. On the patient's side a certain degree of intelligence and self-control, and on the doctor's of skill and experience, is necessary for good results. Failures with insulin and neglect or refusal to use it at all are still quite common, but reflect not on the efficacy of insulin but on the inefficiency of the treatment. Sometimes the cost of the insulin seems a deterrent, but fortunately this can now always be met in this country through the agency of the national health insurance, public assistance, or voluntary hospitals. Money for insulin is well spent from the individual and national points of view, as it restores nearly every case to normal working efficiency.

In considering the relative merits of different methods of treatment the chief question is not whether the patient can live (for all methods assure this) but how he can live best. How can we best insure not only healthy and efficient lives, but comfortable and happily normal ones and a normal expectation of life? The last question is the most difficult to answer, and the one I shall consider first.

EXPECTATION OF LIFE AND THE COMPLICATIONS
OF DIABETES

Insulin has not been long enough in use to answer the first question fully. Ten years of healthy life has already been assured without any ill effects in thousands of cases. But whether this will continue twenty or thirty years, or in the case of a diabetic child fifty or sixty years, only time can show. There are no clear indications against such an optimistic view.

An inkling of the dangers and complications to which such cases are exposed may be gathered from experience of long-standing cases of diabetes. These are mostly the milder elderly cases, because in the past younger ones died too soon to develop complications. What percentage of elderly cases eventually became severe I do not know, because the specialist does not see the mild ones. But

* Read in opening a discussion in the Section of Medicine at the Annual Meeting of the British Medical Association, Dublin, 1933.

I see all too many who, after five to ten years, become really severe, and are threatened by wasting and ketosis requiring insulin. Many more—and these are greater tragedies—develop the following complications before their lives are actually threatened.

The most serious complications are cataract, retinitis, and gangrene, although patients may find neuritis equally trying. The first, which occurs also in the young, is most likely produced by osmotic changes in the lens due to varying hyperglycaemia. Retinitis and gangrene are always associated with *arterial degeneration* in both intimal and medial coats dependent on the diabetic condition. Further evidence of degenerative vascular changes is seen in the high incidence of coronary and cerebral arterial disease in long-standing and poorly controlled diabetes. Raised blood pressure is frequently absent, and hypertension does not seem to be an aetiological factor. I feel the most important problem to be solved for diabetic longevity is the cause of this vascular degeneration and how it can be prevented.

The most popular theory is its production by an excess of blood *cholesterol* from the disordered fat metabolism of the diabetic. This is supposed to lead to an atherosclerosis comparable, at first at least, to ordinary atheroma. Against this theory, I have always felt, is the fact that these mild long-standing cases which develop arterial changes have the most normal blood cholesterol concentrations and, indeed, for many years show little disturbance of lipid metabolism as shown by the absence of ketosis. It is certainly true that blood cholesterol is a valuable indication of total fat metabolism in diabetes, and indicates, when high, a serious derangement of total fat metabolism parallel with a low carbohydrate tolerance. But I feel that more definite proof is necessary before we can accept a raised blood cholesterol *per se* as the cause of diabetic vascular degeneration.

The aetiology is to my mind quite unsolved. Malnutrition of the vessel wall, even when the patient's general nutrition remains good, is a possible factor. And the influence of years of hyperglycaemia, with varying mechanical stresses from a blood with increased sugar content, is another possible though unproven hypothesis. The fact that this diabetic sclerosis mainly affects the vessels of the lower extremity, that the pulses in the dorsalis pedis and the tibial arteries are often obliterated while the radial pulse never is, and that diabetic gangrene never affects the hands, is an interesting unsolved problem.

HYPERGLYCAEMIA

Another problem in the best way to treat diabetics is hyperglycaemia, not temporary, but continued over years. Does hyperglycaemia matter if adequate nutrition is insured in insulin cases? In milder cases it always leads to greater severity and the need for and dependence on more exogenous insulin. Apart from this, is it harmful when the patient has progressed to a nearly constant large dose of insulin and is presumably a total diabetic entirely dependent on injected insulin? It is easy enough with a liberal diet and two large doses of insulin to maintain weight and energy in spite of a blood sugar concentration always two to three times the normal and at certain times even higher. Such patients feel reasonably well in spite of some thirst and polyuria, and ketosis may be entirely absent. Does this condition damage their tissues and shorten their lives? Here again no dogmatic answer can be given until statistical studies of such patients can be compared with a group of better-controlled cases over perhaps twenty or thirty years. But my clinical impression is that, apart from the discomforts of glycosuria and thirst, they are more liable to complications. They certainly develop lens changes at an early age and, apart

from liability to infections, do have retinitis and vascular degeneration more frequently than other cases. Such cases certainly progress to severe diabetes and large doses of insulin, but apart from this the strongest argument against hyperglycaemia is physiological, in that nature has perfected in the normal such a wonderful mechanism to prevent it.

THE GLUCOSE-INSULIN EQUIVALENT

Another important question is the glucose-insulin equivalent, the grams of glucose metabolized by 1 unit of insulin on different diets. It has been frequently claimed, and does appear superficially so, in many published papers that the higher the carbohydrate the higher the glucose-insulin equivalent becomes. For example, with a diet containing a fixed amount of protein and fat and 40 grams of carbohydrate, 30 units may be necessary, an equivalent of 1.3 grams per unit. When 150 grams carbohydrate are given only 50 units may be necessary, an equivalent of three. Such appearances are fallacious, because they neglect the work that insulin is doing in burning glucose derived from endogenous sources. In this respect it is worth mentioning some unpublished experiments I carried out in 1928, of which a typical example is shown in the following table.

Insulin	Carbohydrate grams	Carbohydrate- Insulin	Total Glucose	Glucose- Insulin
20	30	1.5	103	5
30	75	2.5	145	4.9
40	140	3.5	210	5.2
15	0	—	70	4.7

In this severe diabetic with a fasting blood sugar of about 0.25 per cent., the varying doses of insulin necessary to reduce this to normal and at the same time to metabolize different amounts of carbohydrate by mouth are recorded. The protein and fat were kept constant and the carbohydrate and glucose alone need be considered. The first three columns show that when ingested carbohydrate and insulin alone are considered the equivalent steadily rises. But it was found that 15 units were required, when no carbohydrate was given, to reduce the blood sugar to the same extent, by acting on endogenous glucose alone. It was calculated from considerations of the total body fluid and its sugar content that some 70 grams of endogenous glucose were metabolized by this 15 units, a glucose-insulin equivalent of nearly five. When this endogenous glucose is added to the ingested carbohydrate (column 4), the very constant glucose-insulin equivalent in the last column is obtained.

INCREASED CARBOHYDRATE DIETS

We can now pass from these theoretical considerations to the practical changes that have taken place of higher and more normal carbohydrate diets. I shall confine myself to diets for adult diabetics, and shall class these into three groups, supplying low, moderate, and high amounts of carbohydrate. There can be no clear-cut agreement about this definition, but in the present state of diabetic therapy I should define the carbohydrate content of a diet as low when it contains below 80 grams and certainly below 50 grams; as moderate between 100 and 150; as high when much more than this is given. Naturally these three adjectives will mean different amounts to different workers, depending on what they themselves are accustomed to prescribe. I should like to emphasize that, as diabetics can be kept well on all three types of diet, a most important criterion of the success of their treatment is their personal comfort and happiness. We must satisfy the patient, and, if we can,

minimize the troubles of dieting and weighing and calculating grams of carbohydrate, protein, and fat, and total calories. We must try for the comfort of the patient to keep down the number of injections to two and for the sake of expense the total of units per day.

As we have seen, it was some time before insulin greatly changed the low carbohydrate diets of pre-insulin days. In the last few years, however, diets of all descriptions—some containing even normal amounts of carbohydrate (300 grams or more)—have been advocated by numerous workers, all of which cannot be mentioned. I must therefore choose a few investigations which are of special importance for their careful work and extensive nature.

Beginning in 1924, Sansum^{3 4} in America was the first to use high carbohydrate diets in a systematic way, giving from 200 to 360 grams a day. His prescriptions of protein and fat were also high, so that the total calories often reached 3,500. Very large doses of insulin are required—often over 100 units, and even 150 or more. This alone kept me from trying such a method. Sansum and his colleagues claimed that their patients felt much better and certainly were more satisfied with the high carbohydrate. Most, however, became fat—definitely overweight. These workers also showed that carbohydrate could be substituted for fat, though not in equicaloric amounts, without raising the insulin requirements. They state that 100 grams fat (930 calories) can be replaced by 130 grams carbohydrate (533 calories) in this way. In their insulin cases they confirmed the fact established by Allen in pre-insulin days that the pancreatic hormone was concerned not only with the metabolism of carbohydrate but also of total calories and the amounts of protein and fat. We shall see that other work confirms this important fact, that calories from protein and fat increase insulin requirements. There is no experimental proof that fat is converted into glucose before burning and for this reason demands insulin for its metabolism, but clinical experience points to something of the sort. It is also certain that the diabetic, when overweight, requires more insulin than when he becomes thinner, when his own carbohydrate tolerance always rises.

The work of Rabinowitch^{5 6 7} of Montreal deserves special mention from its thoroughness and clarity. For some four years he has treated a large series of diabetics by high-carbohydrate low-calorie diets, containing on the average 250 grams carbohydrate, 70 grams protein, and 50 grams fat—about 1,700 calories. He has shown that patients previously on 50 to 100 grams carbohydrate and 150 grams fat (1,900 calories) require much the same insulin when changed to the high-carbohydrate low-fat and low-calorie diet. He stresses the necessity of undernutrition (as Allen did) to obtain these results, and keeps the patients some 10 lb. under their normal weight. There is no evidence in his papers that diets are varied according to the calorific requirements of different individuals, and no patient's weights are given by which we can judge how many calories per kilogram of body weight they are living on. But, certainly, a man of average weight is receiving with such a diet less than the 25 calories per kilogram usually said to meet only basal metabolic requirements. As soon, Rabinowitch admits, as the patient adds more calories to his diet (perhaps unconsciously) in the form of fat, the high carbohydrate cannot be tolerated without very large doses of insulin, because the diet then becomes practically normal and comparable to Sansum's. Rabinowitch states that to obtain good results his new diet must be followed more meticulously than any other. The element of human frailty must therefore be ruled out, and where delinquency has occurred or is likely to enter in Rabinowitch advocates older diets containing 50 to 150 grams carbohydrate. He claims that these high-carbohydrate low-calorie diets are more satis-

factory to the patients, maintain their energy though not their weight at a normal level, abolish all traces of ketosis, and keep the blood cholesterol entirely normal. Such diets certainly give no temptation to exceed in carbohydrate and, as they are so exclusively carbohydrate, are very cheap. But the fats of the land are excluded. And, where money spent on food is an overwhelming consideration, it must be remembered that the price of calories hardly differs between carbohydrate and fat. A pennyworth of bread provides 900 calories; of margarine, 700 calories.

From the patient's point of view such diets demand constant care in measuring all the food, not only the carbohydrate, but also the protein and fat. A rasher of bacon, an extra egg, or two pats of butter cannot be tolerated. I have not had the pleasure of seeing Rabinowitch's clinic and talking to his patients (they may be very content), but I know such a fatless diet would be an intolerable hardship to diabetics previously accustomed to more fat, and this is what Joslin finds with his patients. We shall return to further consideration of this regime after examining an important recent publication from Edinburgh.

Eason and Lyon⁸ have investigated the problem by putting twenty-nine pedigree insulin cases for alternating periods on diets of fixed protein but varying carbohydrate and fat (carbohydrate 85 to 330 grams; fat 230 to 50 grams) and observing their insulin requirements and clinical condition. They confirmed Rabinowitch's finding that, if the total calories are reduced and kept low by fat restriction, the insulin may be reduced although the carbohydrate is doubled. If, however, equicaloric diets are studied, they found that the higher the carbohydrate the more insulin is required. Although their studies again show that extra fat requires insulin, it needs less than an equal number of calories provided by carbohydrate. They state that it is seldom possible to replace 100 grams fat (930 calories) by more than 70 grams carbohydrate (280 calories). As regards their patients, these naturally liked the high carbohydrate, but missed (subconsciously, no doubt) the total calories. For most of them the really low-calorie Rabinowitch diet was unsuited for prolonged use, as they lost weight and energy. Eason and Lyon came to the conclusion that intermediate diets of 150 grams carbohydrate and 100 to 150 grams fat (2,000 to 2,500 calories) prove most successful and satisfactory. They consider strict weighing of all the diet necessary for insulin cases.

The conclusions which we can draw from the above work are clear and I believe true and ultimate, at any rate until further progress shows up our fallacies. It appears that insulin is concerned not only with the metabolism of carbohydrate but with the total foodstuffs. The lower the calories and total foodstuffs the less insulin is required, and with real undernutrition diets high carbohydrate may be tolerated with little or no insulin. This accords with old experience of the oatmeal "cures" of von Noorden and later "potato" cures, where high and exclusively carbohydrate diets (low in calories) were well tolerated for a time, but did not admit of the addition of fats and protein, demanded by most normal appetites. I personally fail to see the advantage of jam and marmalade in the high carbohydrate diet if a rasher of bacon and an extra pat of butter are anathema. Practically all the published work lays stress on the necessity of weighing or measuring all the food and watching the total calories. But can we not get over this extreme preoccupation with diet and make its care less vigilant, even in the severest insulin case? I think we can, and would like to conclude with a method of doing so which observes the minimum of care with the maximum of ease and normality to the patient.

MINIMUM ESSENTIALS OF INSULIN TREATMENT

I am no advocate of free diets in diabetes in which the patient eats what he pleases. I have purposely tried this and found enormous doses of insulin necessary. I have also watched the effect of uncontrolled diets in a few unrestrainable patients, and seen the difficulties. The following are the essential points that must be observed in an insulin case.

1. The most important is that a *regular amount of carbohydrate* is given, *balanced* by its *correct dose of insulin*. Without this regularity the patient's condition must vary between hyperglycaemia and unpleasant hypoglycaemia. Glucose derived from protein and fat does enter into the insulin requirements, but only slowly, and shows its effect over days or weeks; it is the carbohydrate eaten at a particular meal that immediately balances the dose of insulin. Whether the carbohydrate prescribed is low, moderate, or high it must always be regularized.

2. The minimum of carbohydrate is fixed by the fact that a certain amount must be burned to prevent ketosis. I believe 100 grams carbohydrate are sufficient for this purpose, however much protein and fat are eaten, and smaller amounts are frequently adequate. The minimum is also influenced by the tastes of the patient and the necessity of giving him satisfactory amounts of bread, potatoes, and fruit, etc.; 150 grams carbohydrate are almost always sufficient for this.

3. If high carbohydrate diets are given (over 200 grams carbohydrate) great care is necessary to restrict the total calories provided by protein and fat if very large doses of insulin are to be avoided.

The essential therefore appears to be to give an adequate regular amount of carbohydrate and at the same time to prevent an excessive calorific intake. How can this be done most easily, and yet safely and economically, for the commercial traveller, the daily labourer, and the poor mother with five children, who certainly have no time and opportunity to weigh or measure all their food at every meal and look after the total calories? The following plan has been adopted with most of my cases in recent years, and has worked well. It involves the minimum of trouble.

Several hundreds of insulin cases have been treated successfully without any regard to the total calories of the diet. In such cases I regularize the carbohydrate, most often between 100 and 150 grams carbohydrate, and work out the correct dose of insulin to balance it. The patients eat protein and fat to taste, and this varies with their natural appetites and activities and the stage of their treatment. For instance, it is usual to find that the wasted patient, when first treated with insulin, is ravenously hungry, and will eat enormous quantities of protein and fat as well as the fixed amount of carbohydrate. This excessive hunger seems physiological, and disappears in a few weeks when the nutrition becomes normal after a gain of perhaps 10 or 20 lb.; and later, when a constant weight (probably physiological for that individual) is reached, the appetite becomes entirely normal and no great excess of fat is eaten, seldom over 150 grams a day. It will be found that when more exercise is taken, during holidays for instance, the protein and fat are automatically increased by the dictates of the appetite, which, in my opinion, is usually beautifully attuned to the metabolic requirements.

This treatment is not so casual or unscientific as it may seem to those steeped in years of calories. True, neither the patients nor myself have any exact idea of the total calories. But, though no undernutrition is attempted, the method avoids the great excess of calories that result when high carbohydrate is unaccompanied by great

restriction of fat. The carbohydrate is only a third of the normal individual's, and the calories from this source some 500 instead of 1,500. The protein eaten seldom exceeds 100 grams and the fat 150 grams, a total calorific content of about 2,300 at the maximum. Therefore this method resembles very closely the moderate-carbohydrate rather high-fat treatment which Eason and Lyon found most suitable for the average patient.

The greatest advantage is the freedom of the patient and the minimum of preoccupation with the disease. Only the carbohydrates have to be measured or weighed and the adequate dose of insulin taken. As a rule attention need be paid only to the more concentrated carbohydrates like bread, cereals, potatoes, fruits, etc. The diet staff at my hospital assure me of the improved outlook of patients treated in this way, their increased happiness, and the comparative absence of "food" and "diabetic" complexes.

It may be thought, as the protein and fat vary from day to day and do count in insulin requirements, that it would be difficult to obtain a regular balance with insulin to avoid hyper- and hypo-glycaemia. This is not so, and on second thoughts there is probably little variation from day to day in most people's diet in the amount of bacon and eggs, meat, and butter eaten. Again, changes in insulin requirements depending on protein and fat manifest themselves gradually, probably mainly as the body weight changes. In any case, with the most immutable and completely weighed diet insulin requirements vary from time to time, and there is no such thing as a constant dosage in people leading normal, and consequently variable, lives.

There is nothing really new in this method. Many intelligent patients have discovered it for themselves, and found that they could keep themselves comfortably well with neglect of accuracy over protein and fat as long as carbohydrate and insulin are balanced.

This moderate carbohydrate, free protein, and fat diet is not advocated for all cases. The obese should be reduced by insistence on low calorie and low fat diets, and children, where total calories are more important, are often much better treated by total regulation of diet. Anxious parents, at any rate, feel much safer weighing everything.

The insulin requirements for such diets vary enormously in different patients, as with all diets, but more is certainly required than with low calorie undernutrition diets. I find that the usual severe case treated in this way now tends to need 40 to 60 units a day instead of the 30 to 50 when I used the old line ration scheme with lower carbohydrate and lower and exactly measured calories. The vast majority can be controlled by a morning and evening injection, and I very rarely have to use a third (midday) one. This is an enormous boon to the patient.

In conclusion, I believe that many types and variations of diet work well so long as adequate insulin is given. To obtain the most satisfactory results the treatment can and should be modified from case to case to suit the comfort and habits of the patient. The theoretical problem of the treatment of the *disease* diabetes no longer remains, but only the practical difficulties of making life safe and easy for the *individual diabetic patient*. These will remain until a cure is found.

The latter may be looking a long way ahead, as we do not know yet the aetiology or even the intimate nature of the defect. What is obviously and urgently needed is an insulin effective by mouth, and I look forward to the day when "diabetic" bread will no longer consist of a mess of protein and fat, but will be baked from the finest flour with the requisite amount of insulin incorporated.

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UREA IN HEALTH AND DISEASE*

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In one of his alchemical writings, *The Economy of Minerals*, Paracelsus speaks of "the superfluous nutritional salt not yet digested by the animal decoction when it is driven off into the urine." Such a description might well apply to urea, the chief nitrogenous waste product of the higher animal, and one of the simplest and most widely distributed biological forms of organic nitrogen.

THE FUNCTIONS OF UREA

1. *An End-Product of Protein Metabolism.*—The most obvious use of urea is the provision of a neutral, inert, and very soluble form in which nitrogen can be eliminated from the animal body. Within the organism urea is stable and unlikely to undergo further change; outside the organism it is readily resolved into ammonia and carbon dioxide by the various ureases of the environment, and the nitrogen is able to enter into the life-cycle of the plant. Indeed, from the vegetable point of view the animal's chief end might be said to be the manufacture of urea.

2. *A Diuretic.*—Urea is easily excreted by the healthy kidney, and has been used therapeutically as a natural diuretic. Probably the effect is osmotic and due to the effort of the kidney to keep the urea concentration in the urine below 2 per cent., but there is some evidence that it has a specific action on the renal apparatus. After administration of 30 to 60 grams of urea the urinary volume has been more than doubled, and favourable results are reported in conditions of oedema of cardiac and nephritic origin.

3. *A Galactagogue.*—Addition of urea up to the effective maximum of 150 grams per diem to the diet of cows has raised the milk production over a period of 100 days, the

* Read in opening a discussion in the Section of Physiology and Biochemistry at the Annual Meeting of the British Medical Association, Dublin, 1933.

increased yield in some animals being 6 to 8 per cent. Here again the action is osmotic and part of the general secretagogue effect of the easily eliminated solute.

4. *A Solvent.*—Urea has a solvent and peptizing action on proteins, and can bring about denaturation (Hopkins, 1930). While this effect must be almost negligible at the ordinary concentrations of urea found in health, it may become important in conditions of severe hyperuraemia.

5. *A Precursor of Urinary Ammonia.*—Ammonia formation by the kidney is an emergency factor in the regulation of the H-ion concentration of the blood, and it is suggested, on rather hesitating evidence, that this involves a decomposition of urea in the renal tissue.

Many other speculations have been made regarding possible functions of urea in metabolism, including its ability to replace, supplement, or spare protein in the dietary, but there is no direct evidence that this metabolic reversal can occur.

THE ORIGIN OF UREA

Urea is formed almost entirely by the hepatic deamination of surplus amino-acids. The location of this process has been accomplished experimentally by Bollman, Mann, and Magath (1924), who have been unable to detect any urea formation in dogs after complete removal of the liver.

That small quantities of urea may arise from other sources is shown by the work of Clark, Gaddie, and Stewart (1931) on the metabolism of the isolated frog heart, which oxidizes amino-acids and produces urea and ammonia in traces. Indeed, it seems reasonable to suppose that any tissue capable of metabolizing amino-nitrogen is also capable of degrading it into urea or some precursor of urea, but the general trend of recent work indicates either that this is not so, or that non-hepatic urea is relatively unimportant.

Ureagenesis is an effective and sustained physiological process, and is one of the last functions to fail in liver disease.

Its constancy is illustrated by the accompanying graph showing the half-hourly excretion of urea in the urine over a period of twenty-four hours. The experiment

is one of an unpublished series carried out by Professor J. W. Jessop of Dublin.

THE SIGNIFICANCE OF UREA

Urea is derived chiefly from the surplus amino-acids of the diet. The organism is only able to store these units by building them up into tissue proteins, and as this is restricted by the capacity of the tissues, the unwanted amino-acids circulate in the blood stream and are removed by the liver. The important practical question arises as to the necessity for these surplus units. The adult daily output of urea ranges from 25 to 30 grams, dependent on the consumption of 80 to 90 grams of food protein, which may cost anything from a shilling upwards.

The graph shows: (a) a slight fall in urea excretion immediately after food ingestion, and (b) a steady rise beginning within half an hour after food. Similar variations have been seen in the other graphs. The output rises throughout the day, and is at a higher level at the end of the experimental period. This probably is due to metabolic stimulation accompanying enforced wakefulness. The subject of the experiment was in a condition of equilibrium, and the observations were made while on the normal diet. The urea estimations were made in duplicate by the nitro-metric method of E. A. Werner.