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D. M. Dunlop
B.A., M.D., F.R.C.P.Ed., F.R.C.P.
Professor of Therapeutics in the University of Edinburgh;
Fellow and Former President of the Society.

Abstract
The increasing tempo of change in outlook and way of life is a characteristic of our modern age, and our changing attitudes in medicine keep pace with the rapid metamorphosis of the intellectual and material world around us. When I was asked to write an article for *Res Medica* on diabetes I thought, therefore, that it might be amusing and instructive to contrast my attitude to the disorder twenty-five years ago when I was a young physician with what it is now when I am a middle-aged or elderly one, for in almost every respect the change has been revolutionary.
Twenty-five years ago we regarded the pathogenesis of diabetes as being very simple, however complicated it might be to treat. We knew that the pancreatectomised animal or the animal poisoned with alloxan became diabetic and died but that it could be kept alive by the appropriate administration of insulin. Diabetes was therefore regarded as being due to a simple deficiency of the internal secretion of the pancreatic islet tissue just as primary myxoedema was due to a simple failure of the thyroid to secrete the thyroid hormone.

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CHANGING FASHIONS IN DIABETES

By D. M. DUNLOP
B.A., M.D., F.R.C.P.Ed., F.R.C.P.
Professor of Therapeutics in the University of Edinburgh;
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The increasing tempo of change in outlook and way of life is a characteristic of our modern age, and our changing attitudes in medicine keep pace with the rapid metamorphosis of the intellectual and material world around us. When I was asked to write an article for *Res Medica* on diabetes I thought, therefore, that it might be amusing and instructive to contrast my attitude to the disorder twenty-five years ago when I was a young physician with what it is now when I am a middle-aged or elderly one, for in almost every respect the change has been revolutionary.

Twenty-five years ago we regarded the pathogenesis of diabetes as being very simple, however complicated it might be to treat. We knew that the pancreatectomised animal or the animal poisoned with alloxan became diabetic and died but that it could be kept alive by the appropriate administration of insulin. Diabetes was therefore regarded as being due to a simple deficiency of the internal secretion of the pancreatic islet tissue just as primary myxoedema was due to a simple failure of the thyroid to secrete the thyroid hormone.

We now no longer regard diabetes as being due to the simple failure of this secretory capacity of the beta cells of the islets of Langerhans. Though this may account for some cases it cannot account for all as is shown by the fact that total pancreatectomy in non-diabetics results in a relatively mild diabetes which can be controlled by not more than 40 units of insulin a day, and we know that many diabetics regularly require far larger doses than this. Further, diabetes can be induced by the injection of crude emulsions of the pituitary gland and can be improved by hypophysectomy, and these experimental observations have their clinical analogues in the diabetes of acromegaly and the increased sensitivity to insulin of patients suffering from hypopituitarism. The pituitary growth hormone has been shown to have diabetogenic effects, but the hypophysis also exerts its diabetogenic influence through the stimulant effect of corticotrophin on the adrenal cortical hormones. Thus cortisone given to the hypophysectomised animal or to a patient with hypopituitarism corrects most of the hypoglycaemic effects produced by loss of the pituitary. Further, adrenalectomy or Addison's disease cause a marked tendency to hypoglycaemia and may alleviate a pre-existing diabetes, while adrenal cortical hyperfunction, as seen in Cushing's syndrome, may result in hyperglycaemia. Thus, though the mechanisms responsible for the production and continuance of diabetes remain obscure, there seems little doubt that in many cases lack of insulin is relative rather than absolute. It is probable, therefore, that the term "diabetes mellitus" is a comprehensive one which includes a number of diseases with the common characteristics of hyperglycaemia and glycosuria, just as "anaemia" is a comprehensive term which includes a large variety of disorders characterised by clinical features which are the direct consequence of the diminished oxygen-carrying power of the blood. Indeed,

apart from her mild hyperglycaemia and glycosuria, the obese middle-aged diabetic woman presents few clinical features in common with the young diabetic male: the one suffers from obesity and possibly from pruritus and neuritis, the other from polyuria, thirst, emaciation, weakness, and ketosis.

Though the mechanisms responsible for the failure of the pancreatic internal secetion were obscure we had little doubt, twenty-five years ago, that the failure occurred coincidently with the onset of the symptoms of the disease. We are now more apt to look upon diabetes as a late clinical manifestation of a metabolic abnormality which may in some cases have been operative for many years prior to the onset of the hyperglycaemia and glycosuria with their accompanying symptoms, just as adult tuberculous manifestations may in some cases be the last verse of a song sung to the infant in its cradle. The probability of a preclinical diabetic state is perhaps best exemplified by the obstetrical history of the diabetic woman. As is well known, such women tend to give birth to large babies and there is a high foetal loss rate in diabetic pregnancies, but it is less well appreciated that these same tendencies can be traced in the obstetrical histories of such women for many years before they become clinically diabetic. Thus the foetal loss rate for pre-diabetic periods of twenty years is in excess of the non-diabetic control rate and steadily increases till it reaches a maximum in the five-year period prior to the onset of clinical diabetes. The high incidence of large babies in this pre-diabetic period is also noteworthy. Some 60 per cent. of mothers who eventually become diabetic give birth to babies of 10 lb. or more at some time prior to the onset of their clinical diabetes. Indeed it seems that the heavier the baby the more likely is the mother to develop diabetes, and if she gives birth to an enormous one of 13 lb. the prospects of her developing diabetes are very great.

Thus, it seems that there is a factor conducive to large babies and to foetal and neo-natal mortality which may be active for as long as twenty years prior to the development of clinical diabetes and very active for the five years immediately preceding it. It seems probable that the factor responsible for the high foetal loss rate and the ensuing maternal diabetes has a common basis in some general metabolic disturbance in the mother, and that the development of clinical diabetes is a late manifestation of this disturbance.

Another example of the pre-clinical diabetic state is to be found in the transient diabetes not uncommonly induced in seemingly healthy persons by the development of a severe staphylococcal boil or carbuncle; yet in many such patients their glucose tolerance may apparently return to normal with the subsidence of the infection. The majority, however, develop permanent diabetes in a shorter or longer time.

If we are ever to be able to prevent the onset of clinical diabetes we must be in a position to recognise those who are destined to develop it. The conventional oral glucose tolerance is a rough test which does not give a precise evaluation of glucose tolerance as absorption from the intestine is not completed for a variable time. Thus the rise and fall of the curve do not reflect the true rates of either absorption or disposal as the two processes progress simultaneously. In contrast, following the intravenous administration of glucose, the maximal hyperglycaemia is immediate and the subsequent fall in the blood glucose level is uninfluenced by simultaneous absorption. Analysis of the observed fall in blood glucose by appropriate mathematical methods eliminates a major inaccuracy in the measurement of glucose tolerance and permits it to be expressed in numerical terms. The test can be made even more sensitive by taking advantage of the diabetogenic activity of a single dose of 200 mg. of cortisone administered orally

two hours prior to the injection of glucose. It may be that by the employment of the cortisone loaded intravenous tolerance test the diagnosis of pre-clinical diabetes will be made possible, but it will take years before such expectations can be fully confirmed.

Twenty-five years ago we were entirely occupied, so far as diabetes was concerned, with endeavouring to keep the patient alive for a while and, apart from gangrene, we knew little of its ultimate complications for few patients had lived long enough to develop them. To-day the problem is not so much that of the acute disease as exemplified by diabetic coma, for we know, or ought to know, how to avoid that disaster, as it is of a chronic disorder with a considerable expectation of life which involves a prolonged effort to avoid the chronic degenerative complications which so commonly ensue—retinopathy, nephropathy, neuropathy, and the premature occurrence of cerebral and coronary atherosclerosis.

Thus the common cause of death among young diabetics in most communities which are well organised from a medical point of view is no longer diabetic coma, as it used to be, but uraemia—the result of diabetic nephropathy (the Kimmelstiel-Wilson syndrome). Is the occurrence of these complications to be regarded fatalistically as being due to something inherent in the diabetic process like the large babies of diabetic and pre-diabetic mothers—the inevitable sequel in a shorter or longer time of the diabetic state? Or can they be prevented by care and trouble directed to the control of the metabolic disturbance?

There are many who believe that there is no apparent relationship between the severity of diabetes, the control of the condition by treatment and the presence or absence of complications—that it makes little difference how a diabetic is treated, if he lives long enough he will inevitably develop one or other of them. The protagonists of this view are naturally of the opinion that hyperglycaemia itself does no harm, provided it is not sufficiently gross to cause pruritus or severe polyuria and thirst, and that, provided there is a proper utilisation of carbohydrate, moderate hyperglycaemia and glycosuria do not matter. This led to a revulsion from the extremely meticulous dietetic control of twenty-five years ago to the use of "free diets" in treatment. Patients were allowed to eat what they liked and enough insulin was administered to ensure ample carbohydrate utilisation from the abundant intake. Hyperglycaemia and glycosuria were largely disregarded and the criteria adopted to govern insulin dosage were freedom from hunger, thirst, nocturia, and ketosis, and the maintenance of weight and energy on the one hand and the avoidance of hypoglycaemic reactions on the other. The advocates of this system claim that patients benefit psychologically from this form of treatment through freedom from irksome restrictions imposed upon their daily life; that "each meal which should be an elegant satisfaction of appetite is not turned into a problem in arithmetic and a trial in self-abnegation"; that if complications are inevitable anyway let the patient eat, drink and be merry and control his diabetic symptoms by appropriate amounts of insulin.

The majority of workers, including myself, are now, however, opposed to this point of view. Our experience with "free diets" has been disastrous and we believe that there is a definite correlation between diabetic "control" and the incidence of complications. We believe, therefore, that whatever specific aetiological factors may be causing diabetic complications, the careful control and aggressive treatment of the disorder over the years is an important factor in the prevention or postponement of these complications, and that every effort should be made to restore physiological conditions,

including freedom from glycosuria and a normal blood-glucose concentration as far as this is possible.

Thus the pendulum of medical fashion has tended to swing back again in favour of the careful dietetic control which was in vogue twenty-five years ago, but there are considerable differences in our methods of control. Twenty-five years ago diabetic diets were very low in carbohydrate—seldom containing much more than 100 g. a day—and very high in fat; they were in consequence expensive, highly abnormal, and distasteful to many patients. Nowadays our aim is to give a diet suitable for the particular patient which does not vary much from day to day in its calorie and carbohydrate content so as to match the daily dose of insulin, but in which the carbohydrate is only moderately reduced and the fat only moderately increased. Further, we have come to realise that good control cannot be achieved by urine testing alone but demands frequent estimations of the blood glucose content as well.

A glucose free urine does not necessarily imply a normal blood glucose concentration which we used to think was the case. We then believed that an individual was born with a certain renal threshold for glucose, just as he was born with a certain shape of nose, and that this did not alter throughout life; the great majority of renal thresholds for glucose lay between 160 and 180 mg. of blood glucose per 100 ml.; it was recognised that occasionally a person had a low threshold. We now realise that a diabetic's renal threshold is not fixed for life but may vary greatly from time to time. Thus, in cases of long duration—especially if the patients are atherosclerotic and have been poorly controlled—the renal threshold for glucose frequently rises to considerable heights (300 mg. per 100 ml. or even more in exceptional cases) so that the urine may contain little or no glucose in spite of very significant degrees of hyperglycaemia. On the other hand, some diabetics —particularly pregnant diabetics—develop low renal thresholds for glucose and in them glycosuria may occur in spite of normal blood glucose levels; in such patients any attempt to keep their urine free from glucose is usually followed by hypoglycaemic reactions. Thus, unless the patient's renal threshold for glucose has been ascertained to be approximately normal, efficient treatment cannot be controlled by urine analysis alone, but demands frequent blood glucose estimations as well. The efficient management of the surgical diabetic, the diabetic woman in labour and the patient suffering from diabetic coma also demands facilities for rapid and frequent blood glucose estimations.

Lastly, the treatment of diabetic coma has changed considerably in the last twenty-five years. We realised then as we do now that such patients were profoundly dehydrated and required fluid, but the fluid we gave was glucose-saline; we realised that he required insulin, but the doses we gave tended to be unduly exiguous; and we didn't realise at all that in the recovery phase the patients developed hypokalaemia and were often in desperate need of potassium. Now, we give saline intravenously, at least in the initial stages of treatment instead of glucose-saline; we usually give from 175 to 300 units of insulin spread over the first three hours of treatment; and we administer as a routine 2 g. of potassium chloride every two hours as soon as the patient can swallow, provided urine is being excreted freely. Perhaps it is this latter measure which has done more than anything else to improve our mortality figures in diabetic coma during the last few years, for, as the result of the insulin therapy and the treatment of the dehydration, potassium passes from the extracellular to the intracellular fluids and the serum potassium may fall to extremely low levels. Thus death from hypopotassaemia may occur during the recovery phase from diabetic coma

in spite of the fact that the ketosis and hyperglycaemia have been adequately controlled. I used to think it very unfair that so many of my patients died when I had apparently cured them as judged by the restoration of their blood glucose concentrations to normal and the disappearance of ketosis from their urine and breath.

I could go on for a long time with reflections on our changing attitudes to diabetic problems in comparison to what they were in the early days: there is the greater emphasis on the role of diabetic neuropathy in the causation of trophic lesions on the feet of diabetics, and the realisation that many of the ulcers which we used to think were entirely due to gangrene are really the result of a mixture of angiopathy and neuropathy; the carbohydrate feeds traditionally given to diabetics immediately prior to surgical operations so frequently caused aspiration pneumonia that if it is necessary to give pre-operative glucose at all it is now always given intravenously; the foetal loss rate in diabetic pregnancies which was over 50 per cent. twenty-five years ago has now been reduced to 20 per cent., chiefly by insisting on a Caesarean delivery about the thirty-sixth week; there are all the new insulins, though it may be doubted if globin insulin and the insulin suspensions really represent any very important therapeutic advance over soluble insulin and zinc protamine insulin except for a few cases; and finally there are the exciting new possibilities which arise with the discovery of the oral hypoglycaemic agents, though British medicine is to be congratulated that its approach to these new remedies has been one of conservative caution until their proper place in therapeutics (and it seems at present to be a limited one) has been clarified by long term clinical trials. One could elaborate at length on these and many more changes in diabetic practice, but your editor has wisely imposed some limits on my verbosity.

INTERRUPTED FERTILITY

COLLECTED FROM THE SOCIETY'S ARCHIVES BY C. VAUGHAN RUCKLEY

From "A case by Dr. TAYLOR.....1777."

Mrs Buff, wife of Mr Buff, silk weaver in Fashion Street in Spitalfields, London, aged twenty-seven years, the mother of several Childrine, on 27th of July 1774, having gone her usual time of pregnancy, was attended by her midwife several days, but tne labour pains ceasing, the midwife left her promising to return soon, but did not fulfill her promise, Mrs B. not being delivered of her child, thought she might have a month longer to go & went about her domestic affairs as usual, Xmas following she prov'd with child again & not being delivered of the former one she became uncommonly big and unwieldy, she applyd to several physicians for advice & particularly to Dr. Wyman an eminent man midwife in Aldermanbury, who ordered her a variety of purgative medicines but without relief, in June she sent for me, and after hearing the above narrative I assured her of being with child, & in October following I laid her of a healthy living child, having had an easy natural labour, she recovered very well until the 10th day, she was taken of a violent purging, her stools very offensive and of a dark bloody appearance, having taken some astringent medicines with Diascordium the Diarrhoea ceas'd but was followed by profuse sweats which weakened her considerably & she was obliged to wean the child I had laid her of, the sweats and purging stools having her for 3 months, she was much reduced in her strength, about this time the thigh bone of a child came away in a purging bloody stool. a few days after half a frontis, two months after she passed half of the under jaw having the sockets of five teeth well marked, all these bones were of a brown darkish colour & were voided with purging bloody stools. March 5th a ragged piece of upper jaw came away, she

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