INSULIN SENSITIVITY AT THE ONSET OF JUVENILE DIABETES*

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It is reasonable to assume that the incidence of diabetes mellitus is likely to increase in the future and that, until the aetiology of the disease can be precisely defined and effectively dealt with, radical cure will not be possible. This report is a contribution towards that objective.

Survey estimates give some indication of the prevalence of a disease in a community. The American Diabetic Association has recently estimated that there are some 1,500,000 diabetics of all ages in the USA. This represents a national incidence rate of 0.9% of the American population.1 This may be an underestimate, for there are higher incidence rates reported in less widespread surveys. In a New England town it was 1.7%,2 and in a Californian city 1.6%.3 In 1937 the national incidence in the USA was 0.51%, and the diabetic population has more than doubled in 20 years. Most of this increase is due to the greater longevity of the treated diabetic (there are more elderly diabetics than ever before). It is much more difficult to estimate the influence of the greater genetic transmission of the disease that has resulted from the restoration to very nearly normal of the diabetic's capacity to procreate.

There have been very considerable advances made in research on diabetes in recent years. The chemical composition of human insulin has been determined,4 and it differs slightly from the insulins of other animals.5,6 Despite these species differences there is no cross-insensitivity to the effects of parenterally administered insulin of one animal to another. In some instances, however, such administration provokes immune mechanisms and anti-insulin antibodies are formed.7 Such antibodies do make the administered insulin less effective, but their value to the research worker has been inestimable, since they form the basis of the immuno-assay technique of measuring actual circulating insulin. In some centres as little as 0.1 micro-unit of insulin can be accurately measured.8

At the onset of the disease the plasma of untreated juvenile diabetics contains as much circulating insulin as that of non-diabetic controls.9 Though the fasting plasma insulin levels are similar, the response to a glucose load differs, there being a delayed rise in the insulin activity in the diabetic. When it does rise, it exceeds the level reached by the non-diabetic and remains elevated longer. The mean secretion of insulin is in fact greater in the diabetic patient. Hypoglycaemia does not occur because the insulin is inactivated by circulating antigens.

The onset of diabetes in the juvenile is acute, with ketosis and often rapid progression to diabetic coma, yet insulin assay techniques have revealed normal, or even higher than normal, insulin concentrations in the plasma.10 Treatment is not infrequently followed by clinical remission, during which exogenous insulin requirements drop and the patient may enjoy an interval free from clinical manifestations of the disease. Invariably the disease recurs and, when it does, circulating plasma insulin levels drop, the requirements of therapeutic insulin increase, and the state of "total" diabetes ensues.11

This mode of onset bears a strong resemblance to the onset of experimentally induced diabetes in carnivorous laboratory animals. The daily administration of growth hormone to intact adult dogs and cats induces a clinical state identical with diabetes mellitus. Provided, however, the hormone is soon withdrawn, complete recovery can follow. If the hormone is administered for a longer period the diabetic condition becomes established and persists when the hormone is withdrawn.12 The earliest biochemical change in such animals is a pronounced insensitivity to the action of exogenous insulin. This precedes the appearance of hyperglycaemia and glycosuria by a few days. The insensitivity persists after the clinical state of diabetes has been established, although when the permanent state of diabetes occurs insulin sensitivity rapidly rises again. Plasma insulin rises when growth hormone is administered. It has been suggested as a result of these observations that a temporary oversecretion of growth hormone, too brief to produce acromegaly, might account for some cases of human diabetes.13

Growth hormone, which has this property of inducing

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diabetes, seems to damage the islets of Langerhans. It appears that it stimulates insulin secretion and in the process degenerative changes result, ranging from degranulation to complete hyalinization. Direct proof that a temporary oversecretion of growth hormone is responsible for some cases of human diabetes would depend on the detection of abnormally high concentrations of the hormone in subjects developing the disease, and this would most likely be found in children. Suitable cases for study would need to show sufficient criteria to substantiate a diagnosis of diabetes mellitus together with sufficient evidence that the disease had not progressed to the "total" fixed state.

Three children were studied, and are reported here, because they appeared to fulfil these conditions. A direct assay of growth hormone could not be made in this centre, and only an indirect approach could be attempted. If the clinical and biochemical responses of the laboratory animal to the administration of growth hormone could also be demonstrated in these children, it might reasonably be assumed that growth hormone was possibly involved in the causation of their disease. This would be important in that the parallel behaviour observed in man and animal would no longer be merely a matter of conjecture but a very great probability. If they behaved differently, another explanation would have to be sought. With this end in view, particular investigation of insulin sensitivity was made in these children with early diabetes.

**Case I (A.D.)**

An 11-year-old boy was brought to the outpatient department because his father was convinced he was developing diabetes. For the previous 3 weeks the boy had had polydipsia and polyuria, which he recognized from the illness of his late wife, who had died of diabetes mellitus some years before. There was a definite history of weight loss. A urine specimen confirmed the father's fears and the boy was promptly admitted for further management. His weight was 76 lb., and his height 56½ inches; there were signs of early pubertal development. He was not dehydrated to any significant degree. His breath smelt of acetone and his tonsils were moderately inflamed, but otherwise no abnormalities were found on examination. He was mildly anaemic (haemoglobin 12 G per 100 ml.). The leukocyte count was slightly raised, with a polymorphonuclear predominance. Heaf and Mantoux tuberculin tests as well as routine throat and rectal swabs were negative, and the chest X-ray was clear. Urine sugar was 2% (Benedict's reagent + + + +, and citrate test) and his blood sugar was 408 mg. per 100 ml. There was moderate ketosis on 'acetest' and Rothera's and Gerhardt's ests. Serum electrolytes and the blood urea were within normal limits.

Treatment was conventional, with caloric restriction and injections of soluble insulin. Ten days later a single daily injection of lente insulin was started. Daily insulin requirements fell steadily by about 5 units a day, and finally he was able to do without insulin altogether. There was no glycosuria on an ordinary ward diet, but the glucose-tolerance curve was typically diabetic. A warning that the remission was temporary and recurrence inevitable was issued. The boy's father was instructed to test his son's urine daily and bring him back immediately glycosuria reappeared.

He reappeared 6 months later, having again developed glycosuria and polyuria during the previous 5 days. He weighed 79 lb. and, as on the first admission, no physical abnormalities were detected. There was heavy glycosuria and fasting blood sugar was 333 mg. per 100 ml. Treatment was again followed by clinical remission, and insulin was withdrawn. After a few days' observation, plasma insulin activity (rat epididymal fat-pad technique) was determined. The fasting level was 135 micro-units and it rose to 550 micro-units an hour after a glucose load. The blood sugar rose from 150 to 250 mg. per 100 ml. The previous advice was repeated and he was discharged on ordinary diet.

He was seen irregularly as an outpatient and remained clinically well until 8½ months later, when glycosuria once more recurred and he was again readmitted. The tuberculin test had become positive, with a suggestion of hilar adenopathy, and this was subsequently treated. Before any antidiabetic treatment was given his insulin tolerance and glucose tolerance were assessed and plasma insulin-like activity was repeated. There was no resistance to exogenous insulin. A less convincing remission followed treatment, and he was ultimately discharged on antituberculous therapy, a restricted carbohydrate intake, and a token dose of 4 units of lente insulin daily. He was seen regularly thereafter and his insulin requirements climbed steadily. He is now insulin-dependent, the daily dose being in the region of 20 units.

**Case 2 (B.E.)**

A 6-year-old boy was investigated at our request. He had been quite well, with no diabetic symptoms, but his grandmother was diabetic, his eldest sister was an insulin-dependent diabetic who attended the diabetic clinic, and another non-diabetic sister had been shown to have an abnormally high rise of plasma insulin activity without abnormality of glucose tolerance. He weighed 47 lb. and on examination no physical abnormalities were found. Routine blood count, tuberculin
testing, throat and rectal swabs, and chest X-ray were all negative. His glucose tolerance proved grossly abnormal and his plasma insulin activity rose from 0, fasting, to 370 micro-units after a glucose load. He was considered prediabetic, no treatment was given, and he was discharged on ordinary diet.

Three months later he was readmitted when found to have reducing substances associated with moderately severe impetigo of the knees and one elbow. He weighed 48 lb. and on admission there was very slight glycosuria. Treatment of the impetigo with antibiotics was successful and thereafter there was no further glycosuria for 10 days. Glucose and insulin tolerances were both normal but unfortunately the specimens for repeat plasma insulin activity were inadequate. He remained well on follow-up for a further 4 months.

Case 3 (J.P.)
A girl aged 8 years contracted chickenpox and developed increasing drowsiness. She was admitted to the isolation hospital because encephalitis was suspected. There was marked dehydration, a smell of acetone in the breath, and heavy glycosuria and ketonuria. The blood sugar was 624 mg. per 100 ml. She was treated with intravenous replacement of fluid and electrolytes and injections of soluble insulin, and when controlled was put on lente insulin and dietary restriction. The chickenpox healed and she was transferred to the paediatric wards of this hospital. She weighed 67½ lb. and no abnormalities were found on examination except very early breast development. Routine side-ward investigations gave normal results. Random blood-sugar samples while on insulin ranged between 80 and 258 mg. per 100 ml. The glucose-tolerance curve was of diabetic configuration, but after some days her insulin requirements fell rapidly until insulin had to be withdrawn. Formal insulin sensitivity in the remission period was normal. Glycosuria soon recurred and she was discharged on dietary restriction with a token daily dose of 6 units of lente insulin. She remained well for 4 months on this dosage and was then readmitted because of heavy glycosuria. Apart from early pubescent features there were no physical abnormalities to be found. She was stabilized on 34 units of lente insulin daily and has remained well controlled with doses around this level since discharge.

DISCUSSION
Animal experiments suggest that growth hormone is concerned in the causation of diabetes mellitus. The relationship may be a direct one, for diabetes can be produced in intact adult dogs in as little as 4 - 6 days if the dosage is high enough. The profound insulin resistance that the hormone provokes in the experimental animal suggests antagonism to insulin, and that larger amounts of endogenous insulin may be required to combat the resulting hyperglycaemia.

In these children it is clear that the diabetic state was at first a temporary event. Superficially there was close resemblance to the onset of induced metahypophyseal diabetes in intact adult dogs, but insulin resistance was not demonstrated. If it had been, it would have constituted indirect evidence in favour of excessive secretion of growth hormone. It may be that the period of oversecretion of the hormone is very brief and that the investigation was not coincident with it. Alternatively, the secretion may be at a lower level but act over a longer period than the large concentrated assaults administered to laboratory animals. The large normal size and indications of early puberty at 11 years and 8 years cannot be altogether ignored. The association of the pituitary with the development of diabetes is not disproved by this report. It merely emphasizes that proof will depend on direct assay of the hormone in suitable subjects at the time when it is exerting its effect on carbohydrate metabolism.

In centres where growth-hormone assays can be undertaken, abnormally high serum levels have been found in some cases of diabetes. Untreated overweight diabetics and treated diabetics with retinopathy have revealed the highest levels. As yet there are no reports of studies in children developing the disease. The administration of growth hormone to humans does decrease the sensitivity to administered insulin, but hyperglycaemia has not been produced. In the comparatively small doses required to promote growth in pituitary dwarfs, administration for periods up to 4 years has not altered blood-sugar levels. It may be that larger doses might reproduce the biochemical effects noted in experimental animals. Unlike the adult animal, the young animal does not develop diabetes when the hormone is administered—only excessive growth results. None of the children studied were excessively grown for their age, but it may be significant that the two eldest were at an age when physical growth accompanies the period of sexual development. Despite this they did not show insulin insensitivity. So far as these children were concerned it would appear that indirect evidence of excessive growth-hormone activity was not found, despite the fact that they were studied at the phase of development of their disease when it might have been expected.
SUMMARY

The incidence of diabetes continues to rise. There have been many advances in the understanding of the pathogenesis of the disease. A comparison between the onset of juvenile diabetes and the diabetic state induced by growth hormone in adult carnivores shows close similarity. Investigation of 3 children who were developing diabetes did not reveal either insulin resistance or deficiency in plasma insulin. This is interpreted as indirect evidence against the role of excessive growth-hormone secretion as a factor in the development of the disease in the children studied. Final disproof of the role of growth hormone at the onset of juvenile diabetes will depend on direct assay of that hormone in suitable cases.

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THE USE OF PHENOL AND MYODIL IN THE TREATMENT OF TRIGEMINAL NEURALGIA AND ATYPICAL FACE PAIN


When all symptomatic causes for face pain have been eliminated a group remains in which the pathological process is unknown but in which the pain apparently arises within the nerve. Of this group tic douloureux is one definite subgroup while the remainder are usually classified as atypical trigeminal neuralgia or atypical face pain. Their surgical treatment has presented many problems, not the least of which has been the proper selection of cases suitable for operation. Although most can be relieved by section of the Vth nerve, the resulting corneal anaesthesia presents at least a theoretical disadvantage. Usually this numbness of the cornea is unimportant because sensation remains intact on the other side, though occasionally conjunctivitis or even corneal ulceration may occur. If the motor root is cut unilateral weakness of the muscles of mastication occurs. These complications are rare, however, and in the vast majority of cases section or injection of the Vth nerve provides relief from pain with minimal disability.

A major problem arises when the pain reappears on the other side; then, should surgical intervention become necessary a procedure must be chosen that will relieve the pain without damaging touch fibres, so that corneal anaesthesia is avoided. In true trigeminal neuralgia various procedures have been advocated as alternatives to section of the nerve. These include decompression of the gasserian ganglion by incision of the dura mater overlying Meckel's cave (Taarnhoj1-2), or mere traumatization of the ganglion by pressure (Stender3), or section of the descending tract of the Vth nerve at the medullocervical junction (Sjoquist4). These procedures can be offered to patients in whom a second side has become involved, but the results are only fair (Schurmann5) and for this reason they have not supplanted section of the nerve as a primary procedure. Thus cases with bilateral face pain still constitute a serious problem.

A solution of phenol in myodil of a concentration between 1 in 20 and 1 in 15 has been used by Maher6 and Nathan and Scott7 and others to relieve the pain originating in spinal nerves without producing overt neurological deficit, but the results are inconsistent. For example, Mark et al.8 report a series of cases in which concentrations varying between 1/13 and 1/10 have been used. Some of their patients in whom lower concentrations were used suffered mild complications (weakness, paraesthesiae) while some with higher concentrations escaped. Occasionally the relief from pain was short-lived. In my experience a solution of 1/12 is the most satisfactory; concentrations above this are liable to produce anaesthesia while those below produce indifferent, unpredictable and frequently short-lasting results.

In spinal work the solution is injected into the subarachnoid space and allowed to bathe the affected nerve roots for about 30 minutes by careful positioning of the patients. After this time the phenol is 'fixed' and no further nerve-root destruction occurs if the oil should move elsewhere. This technique was felt to have a place in the treatment of face pain in the hope that corneal sensation and motor power would remain intact while the pain was relieved. The problem is to deliver the phenol and myodil to the Vth nerve in such a way that it bathes the nerve as closely as possible without dilution by cerebrospinal fluid or the interposition of other tissues.

Operative Technique

The Vth nerve can be bathed with phenol and myodil by introducing the solution into Meckel's cave and allowing it to lie in the little sleeve surrounding the nerve. In this series it has been injected under direct vision through the posterior fossa as in Dandy's operation for section of the Vth nerve. This route was chosen in preference to injection through the foramen ovale because dilution with cerebrospinal fluid and the interposition of other tissues such as arachnoid or dura mater can be avoided.