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EXPERIMENTAL RESEARCH ON DIABETES MELLITUS*

BY

F. G. YOUNG, M.A., D.Sc., F.R.S.

Professor of Biochemistry, University of Cambridge

The research which is discussed in this article has been largely directed towards the experimental production in animals of a condition which resembles diabetes mellitus in the human being, together with the examination of the condition in animals and the investigation in human beings of certain points which arise as the result of the animal experimentation. I shall make no attempt to survey the whole of the vast field of research which is relevant, but shall largely consider the investigations of myself and my colleagues, although naturally I shall refer to some other researches.

Experimental Pancreatic Diabetes

The discovery by von Mering and Minkowski in 1889 that surgical removal of the pancreas from the dog results in a condition which resembles severe diabetes mellitus in the human being, together with the observation that degenerative changes are seen in the islets of Langerhans of the pancreas of some diabetic patients (Opie), suggested the possibility that naturally occurring diabetes mellitus was caused by a defect in the mechanism in the pancreatic islets which normally produced a putative antidiabetic hormone.

Despite early failures, including those of Minkowski himself, to prepare the supposed hormone, by 1909 de Meyer (1909) was so confident of its existence that he named it "insuline." When in 1921 Banting and Best at last brought the elusive substance into the light of day the appropriateness of the already dubbed name, with only a slight emendation, was not long in doubt.

Insulin was obtained as a crystalline protein by Abel in 1926. Because the chemistry of proteins was a particularly difficult field of research, it was not until more than 20 years later that a systematic attack on the chemical structure of insulin was started. Then in the comparatively short period of 10 years—1945 to 1955—Dr. Frederick Sanger (see Sanger, 1960) and his colleagues at Cambridge completely elucidated the chemical structure of insulin from ox pancreas (Fig. 1), and subsequently he and his colleagues, of whom Dr. L. F. Smith has been most prominent in this respect, have determined the chemical structures of insulins from a number of species of animals. The clear-cut species differences in the chemical structure of insulin at present known are given in the Table.

Species Differences in the Amino-acid Sequence of the Insulin Molecule

	A Chain				B Chain		
	4	8	9	10	3	29	30
Ox[1] ..	Glu	Ala	Ser	Val	Asp(NH_2)	Lys	Ala
Sheep[2] ..	Glu	Ala	Gly	Val	Asp(NH_2)	Lys	Ala
Horse[3] ..	Glu	Thr	Gly	Ileu	Asp(NH_2)	Lys	Ala
Sei whale[4] ..	Glu	Ala	Ser	Thr	Asp(NH_2)	Lys	Ala
Pig[2] ..	Glu	Thr	Ser	Ileu	Asp(NH_2)	Lys	Ala
Sperm whale[3]	Glu	Thr	Ser	Ileu	Asp(NH_2)	Lys	Ala
Dog[5] ..	Glu	Thr	Ser	Ileu	Asp(NH_2)	Lys	Ala
Human[6] ..	Glu	Thr	Ser	Ileu	Asp(NH_2)	Lys	Thr
Rabbit[5] ..	Glu	Thr	Ser	Ileu	Asp(NH_2)	Lys	Ser
Rat 1[5] ..	Asp	Thr	Ser	Ileu	Lys	Lys	Ser
Rat 2[5] ..	Asp	Thr	Ser	Ileu	Lys	Met	Ser

[1] Sanger and Tuppy (1951); Sanger and Thompson (1953). [2] Brown, Sanger, and Kitai (1955). [3] Harris, Sanger, and Naughton (1956). [4] Ishihara, Saito, Ito, and Fujino (1958). [5] Smith, L. F., unpublished. [6] Nicol and Smith (1960).

In these days when group activity, as opposed to that of the individual, is often rated of highest importance in scientific research, it is particularly pleasing that the problem of the chemical structure of insulin should have been solved not by a "team" of investigators "headed" by somebody, but by an individual who by choice pursued his researches with no more than one or two individuals at a time.

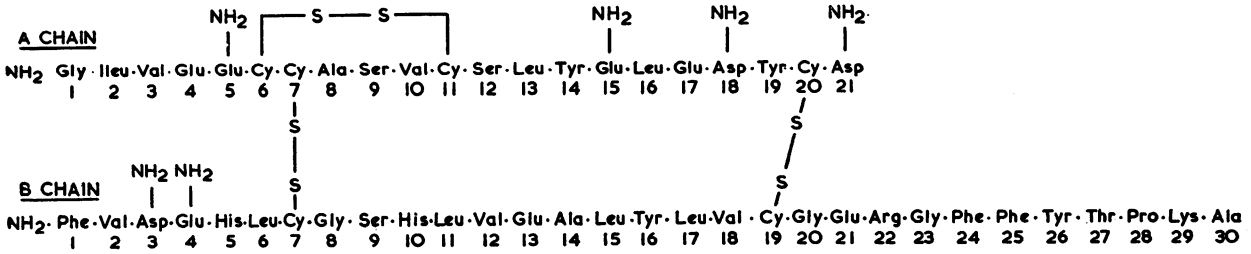

FIG. 1.—Structure of insulin from ox pancreas (see Table above for references).

Fortunately the chemical differences between insulins of different species are not commonly associated with cross-insensitivity to the action of the hormone. The parenteral administration to the human patient of insulin extracted from the pancreas of the ox or sheep, which differs chemically from that prepared from the human pancreas (see Table), normally effects satisfactory control of the human condition.

Because the nature of these chemical differences in insulins is now clear it is not surprising to find that in some instances insulin from one species is quite strongly

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antigenic in another (Stavitsky and Arquilla, 1953; Moloney and Coval, 1955). Antisera to insulin thus produced have been used for the detection and assay of insulin in blood plasma (Yalow and Berson, 1957).

An interesting possibility is that a genetic defect in the pancreatic islets might result in the production of an insulin molecule which differed by perhaps only a single amino-acid from the normal for the species concerned. If such a defect occurred in a part of the insulin molecule which is vital for biological activity, a subnormally active or completely inactive molecule might partly or wholly replace normal insulin. This possibility is purely speculative at the present time (Young, 1959), but if such abnormal molecules exist they may be chemically detectable. An abnormal insulin might, unlike endogenous insulin, be antigenic, with the production of antibodies which reacted with both exogenous and endogenous insulin. A highly insulin-resistant diabetes mellitus might then develop. This is but one of many lines of thought which arise from precise knowledge of the chemical structure of insulin and its species variation.

Despite these possible complexities it is reasonable to suppose at the present time that a high proportion of patients who suffer from diabetes mellitus do so because their islets of Langerhans fail to secrete sufficient normal insulin for their needs. Even a slight deficiency of insulin could result in a small general rise of the blood-sugar level, and the hyperglycaemia so induced might then induce or exacerbate damage to the islets of Langerhans. In this way a severely diabetic condition could develop.

Nevertheless I think that at the present time few would dare to assert that diabetes mellitus always straightforwardly arises because of a subnormal production of insulin by the pancreatic islets. The reason for this caution is the growing evidence for the normal existence in the body of antagonists to the action of insulin, the excessive production of which might result in the development of diabetes mellitus even though the islets of Langerhans initially suffered from no defect.

Antagonists to the Action of Insulin

The fact that a hormone can act physiologically by antagonizing the action of other hormones was firmly established by the investigations of B. A. Houssay and his colleagues in Argentina more than 30 years ago. They found that if the pituitary gland, or its pars glandularis alone, was removed from a depancreatized animal, the diabetic condition of the animal was strikingly alleviated and the life of the otherwise untreated animal greatly prolonged. Subsequently Long and Lukens found that experimental removal of the adrenal glands also depresses the severity of pancreatic diabetes, although some therapy with adrenal hormones may be needed to maintain the adrenalectomized-depancreatized animal in good condition.

Removal of the thyroid gland will also alleviate existing pancreatic diabetes in many species of animal (Houssay, 1948), although the effect of the removal of the thyroid gland is less striking than that of the pituitary or adrenal glands.

The alpha cells of the pancreatic islets secrete glucagon (Sutherland and de Duve, 1948; Foà, Galansino, and Pozza, 1957), a substance which may itself antagonize insulin in some respects, while the antagonism of adrenaline and insulin have long been recognized.

In the time at my disposal I shall single out one of these insulin antagonists for special attention—one of those present in the tissue of the anterior pituitary gland.

Diabetes-inducing Action of Extracts of the Anterior Pituitary Gland

Houssay, Biasotti, and Rietti (1932) observed that the administration to a partially depancreatized dog of a suitable extract of the anterior lobes of ox pituitary glands could induce the appearance of a temporarily diabetic condition.

I began investigations in 1935 with intact dogs as test animals with the idea of isolating the diabetes-inducing pituitary substance and of investigating its mechanism of action. After some initial difficulties I found that in the intact dog the daily administration for one to three weeks of a simple extract of ox anterior pituitary would induce not only a temporarily diabetic condition but one which persisted indefinitely after treatment with the pituitary extract ceased (Young, 1937, 1938). In such animals no signs of the pituitary treatment permanently remained after cessation of the daily injections, apart from the induced diabetes. I can still recall the excitement with which we examined histological sections of the pancreases of these animals which had been prepared by Mr. K. C. Richardson, observing lesions in the islets of Langerhans which ranged from mild degranulation, through hydropsis of various degrees of severity, to complete hyalinization (Richardson and Young, 1938; Richardson, 1940).

A persisting diabetes had thus been induced by a short-lived treatment of a type which could be regarded as initially physiological, though ultimately the excessive emphasis of physiological processes had led to pathological changes in the insulin-secreting mechanism. The possibility could then be considered that human diabetes mellitus might sometimes arise from a short-lived period of hyperactivity of the anterior pituitary lobe, such as might not induce detectable signs of pituitary overaction other than the persisting diabetes. If this were so, search in the diabetic patient for the primary cause of the diabetic condition might prove to be fruitless because that cause might have disappeared by the time the condition had been diagnosed and the patient examined, the persistence of the condition being due to secondarily induced lesions in the pancreatic islets. I shall discuss later more recent investigations which provide support for the validity of this hypothesis.

The discovery of the existence of experimentally induced persisting pituitary diabetes, or metahypophysial diabetes as it subsequently was called, was made in 1937, but it was not until after the war that I and my colleagues were able to identify the substance in our ox pituitary extracts which produced this diabetes. We then concluded that it was pituitary growth hormone, or something closely associated with or formed from it (Cotes, Reid, and Young, 1949; Young, 1953; see also Young, 1939a, 1945). We used intact cats, rather than dogs, in our later experiments on the diabetes-inducing action of growth hormone, since we found that unfortunately this hormone shows its diabetes-inducing effects most constantly in carnivorous animals, and there were no other carnivorous laboratory animals available in sufficient numbers.

In our experiments prolonged daily treatment with growth hormone in doses which induced diabetes in the adult animal does not cause the appearance of a diabetic condition in young growing dogs and cats, but does stimulate excessive growth (Young, 1953). It is only when relatively large doses of growth hormone are given to the adult animal of a limited number of species—as I have just said, mostly carnivorous ones—that its diabetes-inducing activity is readily seen. Unfortunately, in our hands that useful laboratory animal the rat does not develop diabetes when treated excessively with growth hormone alone. Even elderly senile rats respond well to the growth-promoting stimulus of the injected hormone, with no sign of the development of diabetes. Recently the administration of human growth hormone to patients has been found to exert the diabetes-intensifying action expected on the basis of earlier experiments with animals (Ikkos and Luft, 1960).

In addition to growth hormone, pituitary corticotropin can exert a diabetes-inducing action under some conditions (Ingle, 1948; Conn, Louis, and Wheeler, 1948), as also can adrenal steroids with a ketonic oxygen atom or a hydroxyl group at position 11 of the molecule (Ingle, 1941, 1948). Corticotropin and adrenal steroids are in general less effective in inducing diabetes in those species, such as the cat and the dog, in which growth hormone is more active in this respect (Young, 1953; Abelove and Paschkis, 1954; Buse, Gundersen, and Lukens, 1957). The diabetes-inducing action in the dog of the crude extracts of ox pituitary extract used in the early experiments of Houssay and of myself is, I believe, attributable largely to the growth hormone contained therein (Young, 1953).

The diabetes-inducing action of growth hormone probably accounts for the fact that diabetes mellitus often complicates acromegaly, while the similar action of corticotropin and of certain adrenal steroids could account for the diabetes frequently seen in Cushing's syndrome.

Estimation of Growth Hormone in the Blood Plasma of Human Patients

At Cambridge recently Ehrlich and Randle (1961a) have developed a method for the immunological assay of human growth hormone in blood serum which is based on the haemagglutination-inhibition method of Read (Read and Bryan, 1960). The serum-content of human growth hormone, assayed in this way, was found to be abnormally high in each of the seven untreated overweight diabetic patients examined (Ehrlich and Randle, 1961b). It was also elevated in three out of nine untreated underweight diabetics who had no ketoacidosis, and in only one out of nine untreated underweight diabetics in all of whom ketoacidosis was observed. In all of the 18 treated diabetic patients who had no complications the serum content of human growth hormone was in the normal range, but it was elevated in 8 out of 17 diabetics with retinopathy, and in five out of eight pregnant diabetic women. The values in non-diabetic pregnant women were in the normal range (Ehrlich and Randle, 1961a). Ehrlich and Randle (1961b) conclude that in the overweight untreated diabetic both the excessive weight and the diabetes mellitus may result from the observed rise in circulating growth hormone.

The finding that the circulating growth hormone is high in treated diabetic patients with complicating retinopathy is of great interest, and is in accord with the diminution in the severity of retinopathy which has been observed in diabetic patients in whom Sheehan's syndrome develops (Poulsen, 1953) or who are surgically hypophysectomized (Ikkos, Luft, and Gemzell, 1958).

These important observations of Ehrlich and Randle support the view that the oversecretion of growth hormone may be a factor of importance in the development of human diabetes mellitus in at least a proportion of those who suffer from this condition.

Mechanism of Production of Metahypophysial Diabetes

When diabetes is produced in the intact dog or cat by the daily administration of growth hormone the appearance of hyperglycaemia and glycosuria, which do not occur for some days, is preceded by the development of a high degree of insensitivity to the hypoglycaemic action of a small dose of administered insulin (Young, 1939b, 1953). This condition of insulin insensitivity persists after the diabetes develops, and the administration of many hundreds of units of insulin may be needed daily to reduce the blood sugar back to a normal level once it has risen. When the daily treatment with growth hormone ceases and permanent (metahypophysial) diabetes is seen, the sensitivity to insulin rapidly rises (Fig. 2), though it usually remains slightly but significantly below that of the depancreatized dog (Marks and Young, 1939). When the dog with metahypophysial diabetes is depancreatized the insulin requirement usually falls (Marks and Young, 1939) (Fig. 2).

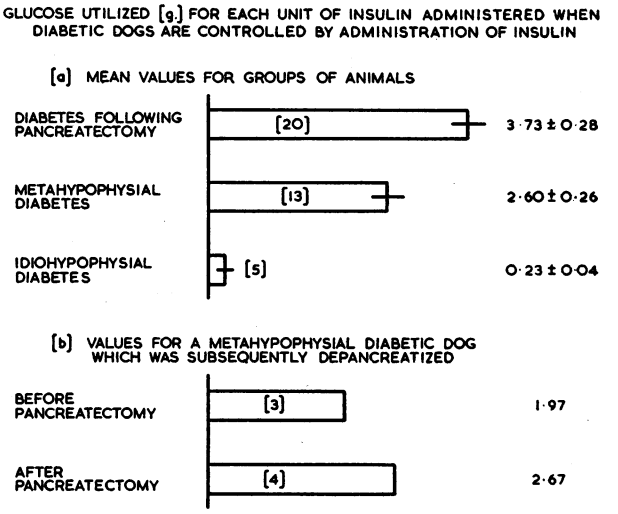

FIG. 2.—Insulin sensitivity of dogs with various types of diabetes. Based mainly on data in Marks and Young (1939). "Idiohypophysial diabetes" is used to indicate the diabetes in a dog under treatment with growth hormone. "Metahypophysial diabetes" is the diabetic condition which persists after the treatment with growth hormone. The figures in parentheses give the total number of observations made.

In the experiments of Mr. H. P. Marks and myself on this topic care was taken to ensure that the disturbed digestive function of the depancreatized dogs did not complicate the results. Such complications were avoided by feeding large amounts of raw pancreas to both depancreatized and metahypophysial diabetic dogs, faecal analyses being made to ensure that the adsorption of food from the gut was similar in both groups (Marks and Young, 1939). Thorogood and Zimmermann (1945) and Rodriguez-Candela (Rodriguez-Candela, 1945;

Rodriguez-Candela, Goñi, Caldeiro, and Gonzalez Carreras, 1947) observed a fall in insulin requirement when alloxan-diabetic dogs were depancreatized, although in these experiments the adequacy of absorption of food from the gut of the depancreatized dogs was not ensured (see Mirsky, Futterman, Wachman, and Persutti, 1951 ; Rodriguez-Candela, 1952).

Though it is small the difference in insulin requirement between dogs with metahypophysial diabetes and depancreatized dogs observed in our experiments appears to be significant. What is the reason for it ? The alpha cells of the pancreatic islets usually remain when metahypophysial diabetes develops, and the secretion of glucagon by them might provide an explanation of this observation, although other possibilities cannot be ruled out.

The gross insensitivity to the hypoglycaemic action of insulin which is seen during the period of treatment with growth hormone can reasonably be related to the reduction in response of rat diaphragm to the *in vitro* addition of insulin when the rat has previously been treated with growth hormone (Cori, 1950). Fig. 3, which

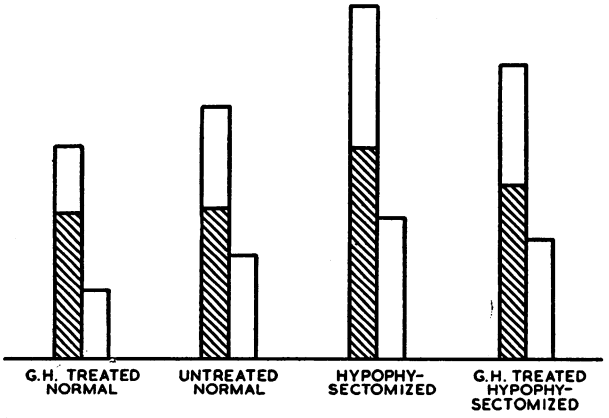

FIG. 3.—Effect of hypophysectomy, and of treatment of the rat with growth hormone (1 mg./day for seven days) on the glucose uptake of subsequently excised and isolated rat diaphragm. GH.=growth hormone. Hatched columns=basal uptake of glucose. Blank columns=additional uptake when insulin (0.5 milliunit/ml. of medium) added *in vitro*. The blank columns are drawn both on top of the hatched ones and on the baseline. The latter facilitates comparison between the various groups of the effectiveness of insulin in promoting glucose uptake.

is based on results published by Manchester, Randle, and Young (1959), illustrates this phenomenon and also the enhanced sensitivity to insulin *in vitro* of diaphragm from hypophysectomized rats, and the reduction in insulin sensitivity when the hypophysectomized rat is treated with growth hormone. Unfortunately, in experiments of this sort the addition of growth hormone *in vitro* to rat diaphragm does not consistently or significantly diminish the sensitivity of the tissue to insulin added *in vitro*. It seems that growth hormone is not itself the insulin antagonist, but something formed from it. The nature of this substance is not at present clear (see Bornstein and Hyde, 1960 ; Vallance-Owen and Lilley, 1961) though it may be formed from growth hormone as the result of a metabolic degradation.

As I mentioned earlier, the diabetic state induced in the dog or cat by the daily administration of growth hormone usually does not appear until after several days of treatment, yet during this latent period gross insensitivity to the action of administered insulin may exist. At the same time mitotic activity, as well as degenerative changes, may be seen in the beta cells of the pancreatic islets (Richardson and Young, 1938 ; Richardson, 1940). This insensitivity to exogenous insulin in the absence of a rise in blood-sugar level (see Young, 1939b) may well reflect a temporary suppression of any effect of the low sensitivity to endogenous insulin on the blood-sugar level by a compensating increase in the rate of secretion of insulin by the islets of Langerhans. Calculation suggests that the pancreatic islets might at this time be secreting many times the normal amount of insulin in order temporarily to keep down the blood-sugar level. Under these conditions the addition of a small test dose of endogenous insulin to that already circulating might well have little or no effect on the blood-sugar level.

If this interpretation of the experimental observations is correct it might reasonably be supposed that when the blood-sugar level ultimately rises under the influence of treatment with growth hormone the rise reflects an inability of the pancreatic islets to continue to secrete insulin at an abnormally high rate. The observed degenerative changes in the beta cells of the islets of Langerhans and the development of metahypophysial diabetes might thus result from permanent damage to the islets occasioned by this temporary overstrain.

These suggestions carry the implication that under the influence of treatment with growth hormone the pancreas may be induced to increase its secretion of insulin. What is the evidence for this ?

Growth Hormone and the Secretion of Insulin

At Cambridge Dr. P. J. Randle has developed a method for the assay of plasma insulin activity (Randle, 1954a, 1956) which is based on the use of the rat diaphragm *in vitro* as first applied to the assay of insulin by Groen, Kamminga, Willebrands, and Blickman (1952). By this means Randle has found that the insulin-like activity of the plasma from acromegalic patients is frequently elevated (Randle, 1954b) while that in patients with hypopituitarism is usually depressed (Randle, 1954c). Randle and Young (1956) found that treatment of the intact cat with growth hormone greatly increased the insulin activity of the blood plasma, but no rise was observed when the depancreatized cat receiving a constant daily dose of insulin was similarly treated. It seemed therefore that the rise in plasma insulin activity under the influence of growth hormone depended upon the presence of the pancreas and was not due to a depression of the rate of inactivation of circulating insulin. The simplest conclusion was that treatment with insulin had indeed stimulated the secretion of insulin by the pancreas. Nevertheless it seemed desirable to obtain more direct evidence by examination of the plasma of the blood draining from the pancreas itself.

Plasma Insulin Activity in Pancreatic Venous Blood

In 1953 Dr. Randle and I together set out to investigate the insulin activity of the plasma of the venous blood which drains from the pancreas of cats that had been made diabetic by treatment with growth hormone. The insulin activity of the blood plasma was assessed by its stimulating effect on the glucose uptake of the isolated rat diaphragm, and by the induced fall of blood sugar when the plasma was injected intravenously into alloxan-diabetic hypophysectomized rats. We found to our surprise that there was less insulin activity in

the plasma from the blood of the portal than in that of the femoral vein, and this was true not only for cats which had been made diabetic by treatment with growth hormone but also for normal control cats (Randle and Young, unpublished results). The problem therefore appeared to be a complicated one and we abandoned it at that time.

Much later I returned to this problem (Young, 1961), using for the assay of insulin activity in blood serum the glucose uptake of rat diaphragm or of rat adipose tissue. In experiments with normal cats I found that the serum of the venous blood draining the pancreas contained less insulin activity than that of the femoral artery (Young, 1961). I was loath to accept the view that the pancreas destroys rather than secretes insulin, and therefore investigated the possible influence of the degree of oxygenation of the blood on the insulin activity of the serum prepared from it. With slaughter-house blood oxygenated or deoxygenated *in vitro* it was found that oxygenation of the blood increased the insulin activity of the serum prepared from it, while deoxygenation diminished it (Young, 1961). Essentially similar results were obtained *in vitro* with blood from the cat, pig, horse, rabbit, and human being. Oxygenation and deoxygenation of separated serum or plasma had no similar action, and the effect appeared to depend upon the presence of the blood corpuscles.

Fractionation of the plasma proteins from oxygenated and deoxygenated blood showed that the biggest difference in insulin activity lay in the gamma-globulin fraction (Gardiner, Martin-Hernandez, and Young, 1960). A smaller difference was observed in the albumin fraction, though this may make an important contribution to the effect of the whole serum or plasma, since in our experiments the albumin fraction constituted about 60% of the total plasma protein (Gardiner *et al.*, 1960).

In some instances the addition *in vitro* to rat diaphragm of the gamma-globulin fraction from deoxygenated blood depressed the glucose uptake of the diaphragm, whereas the addition of the gamma-globulin from a sample of the same blood which had been oxygenated *in vitro* enhanced the glucose uptake of the diaphragm. Thus oxygenation of the blood had transformed an insulin-inhibitory action of the plasma gamma-globulin fraction to an insulin-like one (Gardiner *et al.*, 1960). For this and other reasons it seems probable that the effect of oxygenation is to restrain the activity of the insulin inhibitor, the restraint being released when the blood is deoxygenated or becomes venous. These results provide a reasonable explanation for the observed fact that the biologically assessed insulin-activity of the serum or plasma from the venous effluent of the pancreas is less than that of serum or plasma from arterial blood.

Oxygenation *in vitro* of the venous effluent from the pancreas appears to raise the insulin activity of the serum above that of the serum of arterial blood, but whether treatment of the animal with growth hormone raises it further is a matter still under investigation.

Conclusion

Plasma insulin activity in animals rises when growth hormone is administered under suitable conditions, while elevated values for plasma insulin activity are observed in the human being in conditions where the endogenous secretion of growth hormone is likely to be raised. In untreated diabetic patients, and in many treated patients who have complicating retinopathy, abnormally high levels of serum growth hormone are observed. These observations, together with the fact that the daily administration of growth hormone to dogs and cats for a short time can induce a diabetic condition which persists after the treatment with hormone is stopped, reinforce the view that oversecretion of growth hormone during a short period of time may be one cause of human diabetes mellitus (Young, 1938, 1939a).

For the induction of a persisting diabetes mellitus the oversecretion of growth hormone might need to be of only short duration and need cause no signs of acromegaly. Indeed, the only permanent stigmata might be damage to the islets of Langerhans with consequent persisting diabetes mellitus.

In most instances the primary cause of the diabetic condition—namely, a short period of oversecretion of growth hormone—might well have disappeared before the diabetic condition is recognized and a search for its primary cause begun. In other instances—for example, in diabetic retinopathy—it may linger on in the form of an elevated serum growth hormone content, and this might be a cause of the complications seen in this condition.

The promotion of growth may indeed be but one aspect only of the manifold actions of the metabolic regulator called pituitary growth hormone.

I take this opportunity of thanking the Medical Research Council and the British Diabetic Association for grants which made possible my own researches on the subject of diabetes. I am grateful to Dr. L. F. Smith for gathering the material included in the Table and for permission to include therein some unpublished information of his own, and to Mr. D. C. Gardiner for technical assistance.

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PSYCHIATRIC ASPECTS OF EPILEPTIC AND BRAIN-DAMAGED CHILDREN*

BY

D. A. POND, M.D., F.R.C.P., D.P.M.

Physician, University College and Maudsley Hospitals

Brain Damage

The concept of the brain-damaged child that has been steadily gaining ground in the last few years merits careful and critical examination. Contributions to it have been made by a number of authors—for example, Bradley (1957), Strauss and his co-workers (Strauss and Lehtinen, 1947; Strauss and Kephart, 1955), Bender (1956), and, most recently, Eisenberg (1957), whose review of the symptoms may be taken as one of the clearest expositions of the clinical concept. The symptoms said to be most commonly associated with brain damage in children are hyperkinesis, distractability and short attention-span, lability of mood, antisocial behaviour, low intelligence, and anxiety. These are diffuse symptoms in the sense that they affect large areas of mental functioning, though it is uncertain whether the responsible lesions are diffuse or focal—for example, in the temporal-lobe or mid-brain regions.

The criteria for brain damage appear to be as follows:

1. *History;* which may be of a head injury, encephalitis, anoxia at birth, meningitis, or many another trauma or inflammation of the brain and its coverings. This history may be good evidence of brain damage in the past, but there is the obvious danger of *post hoc, ergo propter hoc,* when it is claimed as the cause of subsequent symptoms.

2. *Neurological Signs and Symptoms such as Hemiplegia or Hemianopia.* These symptoms are signs of damage of a particular part of the brain. Their absence does not signify the absence of brain damage elsewhere, nor does their presence necessarily imply that the damaged area producing these symptoms may also be responsible for the other psychiatric symptoms of which the patient complains.

3. (*a*) *Special Investigations: Physical (A.E.G. and E.E.G.).*—The air-encephalogram is a coarse test of brain damage and sometimes shows normality even when surgery or necropsy has subsequently shown clear evidence of brain damage. The interpretation of the E.E.G. contains even more pitfalls, because there is certainly no E.E.G. change pathognomonic of diffuse brain damage. The findings of an excess of slow activity in an E.E.G. of a patient with a past history of brain damage cannot be regarded as unequivocal evidence of a continued physiological disturbance from that brain damage (see Cobb, 1950). Furthermore, in children there is a very wide variation in standards of normality at any one age, making interpretation still more difficult.

3. (*b*) *Special Investigations: Psychological.*—An adequate survey of the psychological test investigations in brain damage would occupy a lecture in itself (see reviews of Meyer, 1960; and O'Connor, 1958). There would seem to be three main groups of tests. The first refer to the use of special indices in the standard intelligence tests of Wechsler or Binet. Measures of deterioration in adults by comparing the verbal and performance scores are well recognized and standardized. Their application in children is more difficult, since on the one hand wide discrepancies may be found between verbal and performance scores in patients in whom brain damage is not suspected, and on the other no such discrepancies may be found in children with undoubted brain damage. Educated parents can produce a spuriously high verbal score in their backward children.

The second group of tests are those concerned with special psychological functions, of which those related to perceptual anomalies seem to be the most important—for example, the Bender-Gestalt, various form-board tests, etc. Unfortunately, most of these tests have been poorly standardized with inadequate controls. Moreover, often there are no clear correlations between the test results and, on the one hand, the neurological status, and, on the other, personality difficulties and maladjustment (Cruickshank and Bice, 1955).

The third group of psychological tests are the so-called projection tests, of which the Rorschach is the one most frequently used. Many authors have described specific organic signs in the Rorschach test, but these have been equally often denied, and the whole status of this test, and therefore, by implication, of other projective tests, is at the moment under a cloud (Tizard, 1961).

These strictures on the dubious value of most psychological tests should not be regarded as decrying the function of the psychologist himself. In fact, it somewhat increases it in that he or she is essential for the empirical study of any particular case, especially as regards the practical problems of the treatment of a damaged child. By patient investigation of what a child can or cannot do—in, for example, the learning situation—the psychologist makes an essential contribution which cannot be carried out in any other way, but which has a much more dubious connexion with the theoretical problems. For example, the works of Strauss and Lehtinen (1947) and Strauss and Kephart (1955) are deplorably diffuse, irrelevant, and inaccurate, but their insistence on the study of the individual case and their conclusions about teaching methods of handicapped children are important.

There are thus no absolutely unequivocal clinical signs, physiological tests, or psychological tests that can

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