"GROWTH" AND THE DIABETOGENIC ACTION OF ANTERIOR PITUITARY PREPARATIONS

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Joslin (1940) states that about 80% of his adult diabetic patients are, or have been, over weight at the time they come for treatment, and excessive weight is widely recognized as a frequent characteristic of the elderly diabetic patient. White—quoted by Joslin (1940) and by Coggeshall and Root (1940)—finds that at the onset of diabetes a substantial proportion of her diabetic children are above the average height for their age, and many of these show precocious physical development. In discussing these facts Joslin (1940) asks the pertinent question, "In the child growth is vertical, in the adult it is lateral. Is not each type of endocrinal origin?" The results of the experimental investigation described in the present paper indicate, in relation to the evidence already in the literature, that a positive answer might be given to Joslin's question in terms of pancreatic-hypophyseal balance.

The first demonstration of the diabetogenic action of anterior pituitary extract in normal animals was made by Evans, Meyer, Simpson, and Reichert (1931-2) under interesting conditions. Two puppies which had been treated daily with a growth-promoting preparation of ox pituitary gland, and had thereby increased to about twice the weight of control animals, were found to be suffering from polyuria and glycosuria. Two treated litter-mates did not develop this diabetic condition. Using the intact adult dog as a test animal, Young (1939) subsequently found that ammonium sulphate fractionation of a crude extract of ox anterior hypophysis resulted in the precipitation of the diabetogenic principle in the pseudoglobulin fraction, in which it was accompanied by the growth-promoting substance (assayed on the adult intact female rat). Other investigators, using partially depancreatized rats as test objects for diabetogenic activity, have also found a similarity in properties between the growth-promoting and diabetogenic substances (Shibley and Long, 1938). When it is recalled that both Evans, for the growth hormone, and Houssay, for the diabetogenic substance, have strongly emphasized the importance of using absolutely fresh glands for the preparation of active extracts, and of carrying out all procedures at low temperatures, it becomes surprising that more cases have not been recorded of the development of a diabetic condition in the puppies in which gigantism has been produced by treatment with growth-promoting pituitary extracts.

A possible explanation lay in the observation that an adult dog effectively treated with diabetogenic extract for some days eventually developed a refractory state, such that the symptoms of diabetes disappeared during a period of continued similar dosage, though they would reappear if the daily dose of extract were suitably increased (Young, 1937, 1938). It was therefore possible that the puppies treated with growth hormone did exhibit a transient

response to the putative diabetogenic action of the extract, but subsequently became refractory to this aspect of its action, while retaining sensitivity to its growth-promoting effect. It seemed desirable to investigate this point, using extracts with a diabetogenic action demonstrable in normal adult dogs.

Growth hormone preparations induce retention of nitrogen (Evans, 1941); and Mirsky (1939) has obtained evidence that this nitrogen-retaining action may be mediated, in part at least, by the islets of Langerhans of the pancreas. An investigation was therefore undertaken of the relation between the nitrogen-retaining and pancreotropic actions of anterior pituitary extracts, in permanently diabetic animals in which some islet tissue remained. By pancreotropic activity is meant that action of pituitary extracts which induces a rise in islet tissue and insulin contents of the rat pancreas (Marks and Young, 1940) and thus makes more insulin available for secretion.

Methods

Animals.—Normal adult dogs, normal puppies, and adult dogs which had been rendered permanently diabetic by a short period of treatment with anterior pituitary extract (Young, 1937) were used in the present investigation. They were housed in metabolism cages, and daily collections of urine were made under toluene. The amount of food eaten each day was determined by weighing, and was so adjusted that the adult dogs retained about 75 calories/kg./day. The puppies were given a mixed diet *ad lib.*, consisting of raw horse meat, cooked liver, dog biscuits, and milk, with vitamin concentrates twice weekly. The adult dogs received a diet of raw horse meat and liver. All the animals were weighed daily.

Anterior Pituitary Extracts.—A crude extract of fresh ox pituitary tissue was prepared, from glands brought to the laboratory in a frozen condition, by the method before described (Young, 1938), to which further procedures have now been added. In brief, the method consisted in extraction with saline at pH 8.5 in the cold room, followed by spinning on an international centrifuge, clarification in a Sharples supercentrifuge, and Seitz-filtration in the cold room. Bacteriological tests were carried out to ensure that sterility had been obtained. This preparation, which will be referred to as "crude pituitary extract," is highly diabetogenic in normal dogs and cats, and contains most, if not all, of the active principles in the anterior lobe of the ox hypophysis. An unfractionated pituitary extract, which had no detectable diabetogenic action when tested on the intact normal dog but otherwise resembled crude pituitary extract in general activity, was obtained by allowing the sterile crude extract of fresh ox pituitary gland to remain at room temperature for four months. This preparation will be described as extract ND.1. An extract of acetone-desiccated ox anterior lobe powder, which had been stored in the laboratory in a dry condition for some months, was prepared in a manner essentially similar to that for the extract of fresh tissue. This preparation, which was also non-diabetogenic in normal dogs, but resembled crude pituitary

extract in exhibiting manifold activities, will be referred to as extract ND.2. These three unfractionated extracts were of such concentration that 1 c.cm. contained in each case the material extracted from 250 mg. of fresh anterior lobe tissue or its equivalent—i.e., approximately 50 mg. of dried tissue.

A preparation of prolactin, which was obtained by the Bates-Riddle method and which was highly pancreotropic, was used in one experiment. This was the same preparation as that used previously in investigations on pancreotropic activity in rats (Marks and Young, 1940).

All injections were made subcutaneously with aseptic precautions.

Estimations.—Urinary sugar was determined by Benedict's method and urinary ketones by the method of van Slyke. Nitrogen estimations on food, urine, and faeces were arrived at by the Kjeldahl method. Although frequent analyses for the nitrogen content of food were made, these, and faecal nitrogen determinations, were not carried out daily, so that the figures for nitrogen balance are not quantitatively precise, although on the whole the results were agreeably constant. Blood-sugar determinations were made on capillary blood by the Hagedorn-Jensen method.

Action of Crude Pituitary Extract

(a) **Normal Adult Dogs.**—In eight experiments on four dogs (2 male, 2 female) averaging 10 kg. in weight, 5 c.cm. of extract injected subcutaneously each day never failed to produce a substantial glycosuria within seven days. The mean time of the appearance of glycosuria was 5 days (maximum 7, minimum 4) and the average sugar excretion was 23 gm. (maximum 44, minimum 11) on the first day and 58 gm. (maximum 74, minimum 39) on the second day of the diabetic state. The amount of extract required by the subcutaneous route is thus very much less than that necessary when the injections are given intraperitoneally (Young, 1938; Houssay, Foglia, and Smyth,

FIG. 1.—The influence of daily subcutaneous injections of crude anterior pituitary extract on the body weights of puppies. The figures below the arrows indicate the daily dose of extract, in c.cm., given from that day onwards. The dotted lines represent the best straight line fitted to the data for the pre-treatment control period.

1941). We have found our adult dogs remarkably constant in their response to this extract, and it seems reasonable to assume that 0.5 c.cm./kg. (equivalent to 25 mg. dry weight of anterior lobe tissue per kilogramme of body weight), administered subcutaneously each day for at least a week, is more than enough to induce a temporary diabetic condition in adult dogs.

(b) **Normal Puppies.**—Each day four puppies (2 male, 2 female) were given subcutaneous injections of crude extract that were very much larger per kg. of body weight than those required to produce diabetes in adult dogs (Fig. 1). Two of the puppies (Nos. 124 and 126, Fig. 1) received daily doses of

extract which progressively increased from 5 to 20 c.cm./day, and then fell to 5 c.cm. again, while the other two (Nos. 125 and 127) received 5 c.cm./day throughout. Three of the puppies showed no trace of urinary sugar at all, while No. 124 gave a trace on the fifth, sixth, and ninth days of treatment, the maximum twenty-four-hour yield being 1.6 gm. (0.5 gm./kg.) on the sixth day of treatment. No trace of ketone was found in the urine at any time. On the basis of these results we can assume that an average dose of 3.3 c.cm./kg. is not an effective diabetogenic agent in the puppy, this being more than six times the dose fully effective in the adult animal. After a total of 19 weeks' treatment No. 124 had reached a weight of 20 kg., compared with the weight of about 8 kg. which he would have attained if his average pre-treatment rate of growth had been continually maintained over this period. At this time he presented the characteristic features of experimental gigantism in dogs, as described in the classical experiments of H. M. Evans—large paws and head, thick and heavy bones, excessive growth of skin, etc. Up to this time he had been sugar-free despite the continuation of daily injections, but later a gradually increasing glycosuria became apparent. At present, after 23 weeks of treatment, his glycosuria has risen to nearly 200 gm. daily and he has stopped growing, his weight having remained around 20.5 kg. for the last three weeks. Nos. 125 and 126, which have received daily injections for 23 and 19 weeks respectively, have not responded to the prolonged growth-promoting action of the extract so strikingly as dog 124, nor have they yet developed a diabetic condition.

Action of Non-diabetogenic Extracts on Pituitary-diabetic Dogs

If the nitrogen-retaining action of pituitary extracts is mediated by the pancreas, as Mirsky (1939) has suggested, then non-diabetogenic pituitary extracts which are pancreotropic (Marks and Young, 1940) might be expected to cause nitrogen retention, increase in weight, and an alleviation of the diabetic condition of at least a temporary duration in animals which are diabetic but have some secretory islet tissue remaining.

In the experiments carried out in this connexion, a single injection of extract was administered to diabetic dogs after a suitable control period. As might be expected, it was found that the response to any given extract was apparently determined by the intensity of the diabetic condition of the treated animal. Thus treatment with a preparation of prolactin which in the rat test is highly pancreotropic (Marks and Young, 1940) permanently increased the D/N quotient of moderately diabetic dog 115 (Fig. 2, A), inducing a sharp rise in ketonuria, which,

FIG. 2.—Influence of a single subcutaneous injection of various anterior pituitary extracts on the course of diabetes in pituitary-diabetic dogs. The injection was given on the days indicated by the arrows. The initial and final points on each curve represent average values for approximately one week. The intermediate points represent daily values.

Experiment A,	Dog 115:	Injection of 160 mg. of prolactin
" B,	" 118:	" " " 5 c.cm. of extract ND.1
" C,	" 122:	" " " 5 c.cm. of extract ND.2
" D,	" 118:	" " " 5 c.cm. of extract ND.2
" E,	" 122:	" " " " " " " "
" F,	" 118:	" " " " " " " "
" G,	" 118:	" " " " " " " "
		at a time when the dog was receiving 5 units of protamine-zinc-insulin daily
" H,	" 122:	Injection of 5 c.cm. of extract ND.2 when the dog was receiving 15 units of P.-Z.-I. daily
" I,	" 118:	Injection of 5 c.cm. of extract ND.2

however, was only temporary. It must be emphasized that this preparation was non-diabetogenic when tested in large doses in the intact adult dog (Young, 1938), and the same is true of all the extracts considered in the present section. The sustained rise in D/N quotient occasioned by a single injection of this extract suggests that permanent damage had occurred to that pancreatic islet tissue which was still capable of secreting insulin.

Extract ND.1, also pancreotropic in the rat, raised the D/N quotient of mildly diabetic dog 118 (Fig. 2, B) from an initial control value of 1.5 to a final approximately constant figure of 2.3 with a substantial loss of nitrogen and of body weight (B in Table). Again permanent islet damage seems to be indicated.

Table showing the Influence of a Single Injection of Anterior Pituitary Extract on the Condition of Diabetic Dog 118

Exp. (Fig. 2)	Length of Period (Days)	Treatment (Single Injection of Extract)	Food Intake (Cals. Daily)	Sugar Excreted (Gm./Day)	Corrected D/N	Nitrogen Balance (Gm./Day)	Change in Body Weight (Gm./Day)
B	4	Control	1,520	63	1.58	-0.5	0
	7	5 c.cm. ND.1	1,420	121	3.10	-4.2	-100
D	7	Control	1,140	52	1.54	-3.5	-35
	8	5 c.cm. ND.2	1,380	15	0.33	+5.0	+50
F	7	Control	1,850	107	2.32	+1.9	+30
	7	5 c.cm. ND.2	1,910	127	2.45	-3.1	-60
G	7	Control (5 U. of P.-Z.-I. daily)	1,200	33	0.78	—	0
	7	5 c.cm. ND.2 (5 U. of P.-Z.-I. daily)	1,200	14	0.39	+4.2	+100
I	10	Control	900	81	3.60	-2.7	-55
	1	5 c.cm. ND.2	900	99	3.64	-2.9	0
	1	—	620	87	3.19	-13.6	-650

(The data given are the average daily values for the various periods.)

When dog 122, whose D/N quotient was at a level of 3.4, was given a single dose of the same extract the only obvious effect was a sharp but unsustained rise in ketonuria. It is interesting to recall that when pituitary-diabetic dogs which are exhibiting a maximal D/N quotient associated with a substantial ketonuria are given a small daily dose of insulin, the D/N quotient may be largely unaffected while the ketonuria may be strikingly reduced (Marks and Young, 1939). The response of dog 122 to a single injection of the pituitary extract (Fig. 2, C)—a response which is similar to that obtained with many other dogs under comparable conditions—seems to be the converse of that with insulin described earlier, and to indicate that the main effect of the extract has been temporarily to neutralize the action of what little insulin the damaged islets are still capable of secreting.

When dog 118 was in a mildly diabetic state he responded to a single injection of extract ND.2 by a temporary but striking fall in the D/N quotient (Fig. 2, D), with a retention of nitrogen and an increase in body weight (D in Table); but later, when his diabetic condition had become more severe, with a control D/N quotient of 2.3, he resembled dog 122 (Fig. 2, E) and failed to show any very obvious response to an injection of the same extract (Fig. 2, F; F in Table). When, however, the diabetic condition of dog 118 was partially controlled by insulin therapy he again showed a temporary fall in D/N quotient in response to a single injection of the same extract (Fig. 2, G), with nitrogen retention and rise in body weight (G in Table), although the opposite result occurred when dog 122 received an injection of the same extract at a time when his diabetic condition had been reduced to about the same degree of intensity by insulin therapy (Fig. 2, H). Finally, when dog 118 had become severely diabetic, with a control D/N quotient of 3.6 and a daily ketonuria of about 0.3 gm. of total acetone, a single injection of extract ND.2, which previously had temporarily alleviated his diabetic condition, now killed him in diabetic coma (Fig. 2, I), with a rapid loss of nitrogen and of body weight (I in Table) and a terminal blood-sugar level of 0.56%.

From the data for the various experiments on dog 118, given in the Table, it is clear that when treatment with extract alleviated the diabetic condition it also induced nitrogen

retention and an increase in body weight (D and G in Table), but that if the conditions were such that a single injection of extract exacerbated the diabetes it also induced loss of nitrogen and of body weight (B and I in Table).

Discussion

The present observations indicate that if the extracts used by H. M. Evans in his classical experiments concerning the influence of growth-promoting pituitary preparation on puppies had been fully diabetogenic when tested on adult dogs a condition of diabetes would not be expected to develop in treated puppies until after many months' daily injections, if at all. Thus it is possible to produce experimental gigantism without diabetes, even though the pituitary extracts used are diabetogenic in adult dogs or cats.

The results of this and previous investigations show that the same pituitary extract may be essentially growth (weight)-promoting, or essentially diabetogenic, according to the age of the animal and the adequacy of its pancreatic function. In the intact adult animal (dog or cat) both responses may be manifest simultaneously, although the diabetogenic effect ultimately becomes predominant; while in the young puppy the only obvious response to treatment with the same extract is that of accelerated growth. The fact that with normal cats and normal dogs an increase in body weight is associated with the induction of a diabetic condition by the administration of crude pituitary extract has already been emphasized (Young, 1937, 1938). Now, Ogilvie (1937) has presented quantitative evidence that human infants have a greater amount of pancreatic islet tissue in proportion to body weight than adults. If such a difference holds for the puppy and the adult dog, then the resistance of the puppy to the diabetogenic action of pituitary extracts which are highly effective in the adult dog receives a simple explanation. Furthermore, Langfeldt (1920) found that partially depancreatized puppies, which had been deprived of a sufficient proportion of pancreas to provide a reasonable expectation of the appearance of diabetes in an adult dog, not only were free from all symptoms of diabetes for many months after the operation but in some instances showed an increase of sugar tolerance. Eventually, however, the sugar tolerance declined and a progressive and ultimately fatal diabetes became manifest. The present results concerning the diabetogenic action of anterior pituitary extracts in puppies are in many ways analogous to those of Langfeldt.

The results of our experiments on the influence of pituitary extracts on diabetic adult dogs (Fig. 1 and Table) are consistent with Mirsky's idea that the nitrogen-retaining action of the extract is mediated by the islets of Langerhans, but it should be pointed out that Gaebler and Galbraith (1941), as the result of investigations with completely depancreatized dogs, do not believe that pancreatic insulin is the only factor concerned. Indeed, Gaebler and Robinson (1941) have recently found that on depancreatized bitches receiving a constant dosage of insulin prolactin exerted only a mild diabetogenic action but induced some storage of nitrogen. Clearly some action other than a pancreotropic one was exerted by the pituitary preparation in this instance. The present results are not incompatible with such an action, but under the conditions of our experiments it seems reasonable to assume that the main nitrogen-retaining action of the extracts used was mediated by the pancreatic islets. If this is so, the differences in response to the same extract with differences in intensity of the diabetic condition can be reasonably explained in terms of two antagonistic effects—pancreotropic and diabetes-intensifying (diabetogenic ?)—of the extract, the first tending to induce secretion of insulin with nitrogen retention and an increase in body weight, while the second

intensifies, or tends to intensify, the diabetic condition, presumably by suppression of carbohydrate oxidation, etc. (Russell, 1938), or perhaps by increased sugar formation from fatty acids (Soskin, 1941). If the pancreatic islets are capable of responding to the pancreotropic action of the extract to a sufficient extent when the diabetes is uncontrolled (exp. D, Fig. 2 and Table), or after it has been partially controlled by insulin with consequent rehabilitation of islet tissue and insulin storage (exp. G), then the diabetes-intensifying action of the extract may be completely overcome (however, cf. exp. H), so that treatment with the extract causes temporary alleviation of the diabetic condition, with an increase in body weight and storage of nitrogen. But if the islets cannot respond to the pancreotropic action of the extract to such an extent the extract may have no obvious effect (exp. F, Fig. 2 and Table), or may cause an intensification of the diabetic condition which may be only temporary (exp. C and H) or may lead to death in coma (exp. I). With an extract possessing enough diabetes-intensifying activity, a suitable animal may show a persistent exacerbation of the diabetic condition (exp. A and B, Fig. 2) which is presumably associated with permanent damage to the tissue of the pancreatic islets. Gaebler (Gaebler and Zimmerman, 1939-40) found that pituitary extracts which caused growth and nitrogen retention in normal animals showed a marked diabetogenic action in depancreatized thyroidectomized bitches receiving adequate insulin therapy. Phloridized animals reacted, on the other hand, by a rise of body weight and nitrogen retention, with diminished glucose excretion and a constant D/N quotient (Gaebler and Zimmerman, 1939-40). In connexion with the action of our extracts in causing temporary alleviation of the symptoms of pituitary-diabetic animals, with a fall in D/N quotient, it is interesting to note that Haist, Campbell, and Best (1940) find that when such dogs are given a series of injections of crude pituitary extract during a period of fasting, together with very large injections of insulin at frequent intervals, the sugar tolerance of the animals may subsequently show substantial improvement.

It is undesirable to enter here into a discussion of the identities of the active principles concerned, but it should be pointed out that the results indicate that the pancreotropic factor in anterior pituitary extracts is not identical with the diabetes-intensifying factor.* Thus in experiments B and D (Fig. 2 and Table), in both of which dog 118 was initially at the same level of intensity of diabetes, a single injection of one extract induced temporary though marked alleviation of the diabetic condition (exp. D), whereas a different extract raised the D/N quotient and apparently caused permanent damage to islet tissue (exp. B). It therefore seems that the two factors—pancreotropic and diabetes-intensifying—are present in different proportions in these two extracts, and thus cannot be identical. Nevertheless, differential inactivation of different active groupings carried by the same (protein ?) vector cannot be left out of consideration, and the same possibility applies to the previously demonstrated non-identity of the pancreotropic and diabetogenic (intact dog) factors (Marks and Young, 1940). But as we have no evidence on this point it will not be further considered.

Although extracts which are devoid of diabetogenic activity when administered in large doses to the intact dog are capable of intensifying the diabetes of diabetic animals (cf. also Long, 1937), we do not know whether extracts

with diabetogenic activity differ quantitatively or qualitatively from those with only diabetes-intensifying action in the diabetic animal, but it should be emphasized that diabetes-intensifying activity can be completely masked if an extract possesses enough pancreotropic activity and the treated animal has enough responsive islet tissue (exp. D, Fig. 2 and Table).

The presence in the human infant of a large proportion of islet tissue (Ogilvie, 1937) is probably associated with the importance of insulin for nitrogen retention, etc., during the period of growth. If an infant were submitted to a long period of low-grade pituitary overaction the pancreatic islets might at first respond with hypertrophy, so that the child would possess capacity for a greater degree of nitrogen retention and growth. The islets might be incapable of sustaining indefinitely such an intensified activity, and once the general blood-sugar level rose irreparable derangement of islet function might result in persistent diabetes. In the adult person the hypertrophic phase of islet response would, analogously, result in an increase in body weight, and it is of particular interest that Ogilvie (1933, 1935) found that a large proportion of the obese subjects he examined revealed hypertrophy of the pancreatic islets. If such a condition is a pre-diabetic one an extra-pancreatic cause of the diabetes seems extremely probable. Is it therefore unreasonable to suppose that the increase in weight of the pre-diabetic human adult may have an origin similar to that seen in the normal adult dog (and cat) treated with anterior pituitary extract—namely, a slight, and possibly ill-sustained, increase in anterior pituitary action? Such a slight increase in pituitary activity as would be necessary to induce a rise of body weight would not necessarily be associated with obvious symptoms of gigantism or acromegaly; nor would it be expected, at least in the majority of cases, to endow the plasma of the patients with anti-insulin activity, demonstrable in tests on rabbits. Even in diabetes associated with frank acromegaly, insulin sensitivity is comparable to that found in normal diabetes (Coggeshall and Root, 1940). Although this question lies outside the scope of the present investigation, it may be suggested that where obvious adiposity of the human pre-diabetic adult exists it may well arise, to some extent at least, from changes in dietary habits (cf. Himsworth and Marshall, 1935; Richter and Schmidt, 1941) possibly resulting from the inhibition of glucose oxidation by pituitary principles (Russell, 1938).

Conclusion

If the above arguments be accepted the pre-diabetic increase of height in children and of weight in the adult can be regarded as a reactive or protective mechanism for the storage of the carbohydrate of which the oxidation is suppressed, and of the nitrogen which is retained, under the influence of anterior pituitary action. The expansive capacity of the adult is definitely limited, and unless the child is capable of sustained excessive growth (the limit to which may be the capacity of the islets to hypertrophy) there will come a point, as was probably the case with dog 124, at which the carbohydrate the oxidation of which is inhibited can no longer be completely stored in the form of extra body tissue. Sugar then leaks into the blood stream, and despite a subsequent and complete subsidence of pituitary overactivity, permanent stigmata may remain in the form of islet lesions and a persistently diabetic condition. It is interesting to note that the rat, which is capable of substantial and sustained response to the growth-promoting action of pituitary extract even in ripe old age, is almost completely resistant to the diabetogenic action of crude pituitary extract (Young, 1938), although sensitivity can be induced by partial pancreatectomy (Long,

* The word "diabetauxetic" (Greek *αὐξέειν*, to increase), analogous with "diabetogenic," might be useful to describe factors which are capable of intensifying the diabetic condition where diabetes already exists but which are not obviously diabetogenic in suitable intact animals. Similarly, "diabetostatic" might be used to describe factors capable of alleviating the intensity of a diabetic condition by inducing the pancreas to secrete more insulin.

1937, 1939). The above interpretation of experimental findings cannot in any sense be considered as attempting to exclude the possibility that clinical diabetes may result, in some instances, from primary changes in the pancreatic islets—e.g., those which follow interference with the pancreatic blood supply, and in haemochromatosis (cf. Warren, 1938). Nevertheless, the large number of cases of diabetes in which a definite increase in the mass of the body is apparently a proleptic feature may reasonably be supposed to result from a pancreatic-pituitary imbalance occurring at a level of pancreatic islet activity higher than that operative in the normal animal.

Summary

When puppies are treated daily with doses of crude pituitary extract greatly in excess of those required to produce diabetes in adult dogs they respond with an increased growth rate but do not exhibit symptoms of diabetes. When one puppy was treated daily for nearly five months it eventually became intensely diabetic, and then stopped growing despite continuation of treatment.

When adult dogs that have been rendered permanently diabetic by a short period of pituitary treatment are given a single injection of pancreotropic pituitary extracts, which produces no detectable diabetogenic activity in normal adult dogs, the response may be a transitory attenuation of the diabetic condition with nitrogen retention and increase of body weight, or an exacerbation of the diabetes with loss of nitrogen and of body weight; intermediate responses were also obtained. These differences in response are believed to result largely from differences in functional capacity of pancreatic islet tissue.

It is suggested that an increase in body weight, associated with an increase in function of the pancreatic islets, can be regarded as neutralizing, for a time at least, the diabetogenic influence of the anterior pituitary gland. It is therefore possible that the excessive weight of the adult diabetic patient and the abnormal height of the diabetic child (White) indicate an increased pituitary function which may be of temporary duration only, and of which the diabetogenic action may be completely masked for a time by a protective increase in pancreatic islet activity, induced by the pancreotropic action of the gland. Such a condition might lead first to an increase in the mass of the body and eventually to diabetes.

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TREATMENT OF PULMONARY TUBERCULOSIS BY THORACOPLASTY

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Pulmonary tuberculosis is a disease whose incidence rapidly increases during wartime, and it is important in the present situation that the treatment of this condition should remain in the forefront of discussion. From the public health point of view no patient who is suffering from pulmonary tuberculosis should return to work until his sputum is negative. In our crowded factories and offices any such person with a sputum positive for tubercle bacilli is an anachronism, and subversive both to the health of the community and to the war effort. Under the present conditions of long hours of work, continued stress, and minimal nutrition the dissemination of the disease from one such focus may be considerable.

Thoracoplasty is applicable as a line of treatment to only a small percentage of cases of pulmonary tuberculosis. The results are, however, satisfactory in that in most cases the patient, previously a public menace, becomes non-infective and is able to return to some form of useful occupation.

The following is an account of the indications for thoracoplasty in the treatment of pulmonary tuberculosis as used by the team working at the surgical clinic of the Lancashire County Council Tuberculosis Service at High Carley Sanatorium, Ulverston.

Indications for advising Thoracoplasty

This is probably one of the most difficult problems in the whole of surgery. Only by the closest team-work between the surgeons, the staff of the sanatorium, and the anaesthetist can these cases be accurately assessed. The cases are divided into two groups—those regarded as “good risks” and those as “justifiable risks.” The latter group will contain a number of patients suffering from advanced disease in which the risks of thoracoplasty are greatly above the average. These risks are, however, permissible because there is a definite possibility that by running them the disease may be arrested, and because by no other method of treatment can the patient's life be saved. Apart from the consideration of the individual patient, there is another cogent reason why the immediate and ultimate chances of the patient must be most fully weighed. Sanatorium life is such an intimate one that every patient is fully aware of the results of operative treatment on others, and in order that those in the “good” class shall have no misgivings as to the outcome of their operation the fullest confidence in the results of thoracoplasty must be maintained.

There are certain general principles which influence the selection of cases:

1. The tuberculous lesion must be undergoing fibrosis and must not be in a state of acute exudation. Rapid compression of the lung, such as occurs by thoracoplasty, is likely, in cases with an acute exudative lesion, to cause a rapid dissemination of the disease with infiltration of the same or opposite side. If, however, the disease is in a reparative stage—i.e., under-