STUDIES ON THE INFLUENCE OF THE ANTERIOR LOBE OF THE PITUITARY ON CARBOHYDRATE METABOLISM.

By

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Section One.

The Influence of the Anterior Lobe of the Pituitary on Carbohydrate Metabolism.

Introduction. It is now certain that there exists a relationship between the anterior lobe of the pituitary and the metabolism of carbohydrate, but so much experimental work has been carried out in this field that a review of the voluminous literature would be out of place as an introduction to this investigation. Long before such great interest was taken in the subject it had been suspected on clinical grounds that the anterior lobe of the pituitary exerted an influence on carbohydrate metabolism. Borchardt (1908) and Cushing (1911), among others were interested by the high incidence of diabetes mellitus in cases of acromegaly and studied the relationship closely but were inclined to attribute the principal role to the posterior lobe of the pituitary. Indeed it was not until Houssay and his school began to publish a long series of papers dealing with the importance of the anterior lobe that interest was stimulated and the subordinate part played by the posterior lobe established. This work was for the most part published as short notes without much detail but latterly it was conveniently summarised (Houssay and Biasotti, 1931a; Houssay, 1936, 1937) with the result that other workers became interested in the subject. These subsequent investigations have tended, on the whole, to confirm and substantiate the work of the Houssay school.

It may be said that the majority of investigations on this subject have fallen under three headings: the metabolism of the hypophysectomized animal; the metabolism of the hypophysectomized-depancreatized animal; and the effects of the injection of extracts of the anterior pituitary gland into laboratory animals. It is with the results of injection of pituitary extracts that we are concerned in the present investigation and no reference will be made to the literature on the other subjects mentioned unless it has a direct bearing on the problem at issue.

Numerous reports have been published dealing with the influence of various preparations of the anterior lobe of the pituitary on carbohydrate metabolism, and not infrequently these reports have been contradictory. In general three types of action have been described: extracts with a hypoglycaemic or 'pancreotropic' action; with an immediate, slight, transient hyperglycaemic action; with a delayed, prolonged hyperglycaemic action. This last action has been termed 'diabetogenic' by certain authors.

The Hypoglycaemic or Pancreotropic Action. Anselmino and others (1933) have claimed that the injection of a crude anterior pituitary extract into young rats produces a marked increase in the size and number of the islets of Langerhans in the pancreas. This result they attributed to the presence of a pancreotropic substance in the extract. Continuing the study of this phenomenon Hoffmannand Anselmino (1933) found that the extract not only produced a hypertrophy of the islet tissue but also caused a fall

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in the blood sugar level occurring immediately after the injection had been made, and apparently due to a stimulation of the secretion of insulin. Confirmation of these findings has not been obtained by other investigators and indeed entirely negative results have been published (Leyton and Jones 1936; Elmer and others 1937). Richardson and Young (1937) were unable to produce islet tissue hypertrophy in rats with extract prepared in the way described by Anselmino and Hoffmann, although they were able to produce this effect with extract prepared in another manner. They were nevertheless unable to produce any alteration in the blood sugar level by injecting this extract into rats. It seems reasonable to conclude from the published work on this subject that further positive evidence is required before the existence of the 'pancreotropic' substance of Anselmino and Hoffmann is accepted. The significance of the findings of Richardson and Young will be considered later.

The Immediate, Slight, Transient Hyperglycaemic Action.

Many observers, and in particular Lucke (1933), have described an immediate rise in the blood sugar following the injection of anterior pituitary extract, but according to Houssay (1937) the hyperglycaemic produced in this way is faint, inconstant and transitory and bears a close resemblance to that produced by injecting extract of the posterior lobe. Russell (1938) referring to this immediate hyperglycaemic action asserts that in no instance where this effect has been noted has the action

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of the posterior lobe been definitely excluded, and concludes that it does not appear to be established that the anterior lobe has any immediate hyperglycaemic action of its own.

The Delayed, Prolonged, Hyperglycaemic Action. The longer lasting hyperglycaemic effects produced by anterior pituitary extracts were first described by Johns and others (1927), but it was not until some four years later that confirmation of this finding was obtained when H.M. Evans and his co-workers (1931) found that 2 out of a group of 4 dogs developed glycosuria during a course of injections of a growth hormone of the anterior lobe. Thereafter a number of reports appeared in quick succession and the action of crude extracts of the anterior pituitary in producing hyperglycaemia in dogs was described by E.I. Evans (1933), Barnes and Regan (1933), Biasotti (1934a), and Shpiner and Soskin (1934), while Baumann and Marine (1931) obtained similar results in the case of the rabbit. On the other hand Russell (1938) reported unsuccessful attempts to produce hyperglycaemia in this way in normal dogs and rabbits, except in a few instances in which the animal in addition suffered from severe reactions, caused by the injection of large amounts of foreign protein in the extracts used. This observer however did not go so far as to say that the hyperglycaemic effect reported by others was merely the result of a severe foreign protein reaction, but emphasized the fact that the 'diabetogenic' substance was an extremely labile/

labile one and might easily be destroyed in the preparation of the extract. In view of the fact that a permanent diabetic state has been produced in normal dogs by the injection of extracts of the anterior lobe (Young, 1937), it can hardly be doubted that such extracts possess hyperglycaemic properties in themselves quite apart from any possible effect produced by a reaction to foreign protein. However, even if it is granted that there is an element of doubt concerning the existence of a definite hyperglycaemic action in the extract per se in the case of intact animals, there is very convincing evidence of its presence when published reports concerning the action of extract on wholly or partially depancreatized animals are considered. Houssay and Biasotti (1931b) found in the case of the toad that as regards hyperglycaemia the extract was especially active in the partially depancreatized animal. Similarly Bennett, Hopper and Linford (1938) obtained uniformly positive results in partially depancreatized dogs. As is to be expected from these findings many observers have found that complete removal of the pancreas increases the hyperglycaemic activity of extracts of the anterior pituitary. In summing up the evidence on this point Russell says that it can be concluded that anterior pituitary preparations do possess a 'diabetogenic' action, but that the presence of sufficient pancreatic tissue, as well as perhaps some other conditions, may mask its effects in normal animals. This statemnet sums up the matter admirably and can well be adopted as the final word on the question at the moment, especially as it agrees well with the experimental findings obtained in human subjects as will be detailed later.

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The Mode of Action of the Anterior Pituitary on Carbohydrate Metabolism. It is necessary to consider briefly the mode of action of the anterior lobe of the pituitary so as to understand the effects produced by the injection of extracts of the gland but, as there is as yet no settled opinion on this problem, the discussion will be brief and only the more important observations will be noted. The most widely accepted view is that advanced by the Houssay school (Houssay 1936) who are of the opinion that the anterior lobe produces its effects by stimulating the process of gluconeogenesis. There are many arguments in favour of this hypothesis although it must be admitted that certain experimental findings are difficult to explain on this basis. The principal evidence in favour of the Houssay hypothesis may be outlined as follows:

(1) Removal of the hypophysis causes a marked amelioration in the diabetes which results from removal of the pancreas in experimental animals. This finding has been confirmed repeatedly by many groups of workers (Houssay and Biasotti, 1930; Barnes and Regan, 1933; Biasotti, 1934b; Kutz, 1934; Mahoney, 1935; Chaikoff, Gibbs, Holtom, and Reichert, 1936; Shorr and others, 1936), and has been explained as being the result of a diminished formation of new carbohydrate following the hypophysectomy. The work of Long and Lukens (1936a) in particular provided some experimental evidence in favour of this explanation. These investigators observed that when extract of the anterior pituitary was given to hypophysectomized-depancreatized cats the increased excretion/

excretion of nitrogen which followed made it possible to account for the increase in glycosuria on the grounds of gluconeogenesis from protein.

(2) If hypophysectomized dogs are given phlorizin they do not excrete as much glucose and nitrogen as do intact animals, and this may be explained if it is supposed that gluconeogenesis is diminished or suppressed by removal of the hypophysis (Houssay, Biasotti, Benedetto and Rietti, 1933).

(3) Hypophysectomized animals are hypersensitive to the hypoglycaemic action of insulin and respond to about one tenth part of the dose required to produce an effect in the intact animal (Geiling and others, 1927; Houssay and Magenta, 1927; Hartman and others, 1930; Daggs and Eaton, 1933; Corkill and others, 1933; Barnes and others, 1934; Scott and others, 1934; Chaikoff, Reichert, Larson and Mathes, 1935; Chambers and others, 1935; Pencharz and others, 1936). This feature has been explained by supposing a condition of insufficient gluconeogenesis in the reactive phase following the injection of insulin, but it must be recognised that no direct evidence of the existence of this abnormality has been advanced, and the idea expressed is only a convenient extension of that proposed as an explanation of other features of the hypophysectomized animal.

(4) Animals in which the hypophysis has been removed are very subject to the most profound hypoglycaemic crises which may terminate fatally if not treated energetically. It has been generally recognised that fasting is the essential factor in the production/

production of this state (Corkill and others, 1933; Mahoney, 1934; Collip, 1935; Soskin, Missky, Zimmerman and Crohn, 1935; Russell, 1936; Long and Lukens, 1936b; Ball and others, 1937; Russell and Bennett, 1937). If, as is generally believed, the normal blood sugar levels are maintained during fasting by the process of gluconeogenesis, then a suppression of gluconeogenesis following removal of the hypophysis would explain the occurrence of severe hypoglycaemia as the result of abstention from food.

It has also been found that when animals from which the hypophysis has been removed are fasted, even for short periods such as 6 or 8 hours, in addition to a fall in the blood sugar there occurs a fall in the muscle and liver glycogen levels, much greater than that which occurs in the normal fasted animal. This excessive fall in the carbohydrate levels of the body can be avoided if a small part of the anterior pituitary is left in situ, or if the animal is given anterior pituitary extract (Fisher and others, 1936; Russell, 1936; Russell and Bennett, 1937). A similar explanation has been advanced for this observation, that is to say the carbohydrate levels of the body are maintained during fasting by a formation of new carbohydrate and in the absence of the hypophysis, gluconeogenesis being diminished, the muscle and liver glycogen cannot be restored, with the result that there is a considerable depletion of the carbohydrate stores of the body. The presence of even a small portion of the anterior lobe of the pituitary, or the injection of extract of the gland, is sufficient to correct this failure of formation of new carbohydrate/

carbohydrate and so the levels are maintained at a more normal figure.

It will be noted that the evidence advanced in favour of the Houssay hypothesis is largely indirect, and there is little direct proof that the anterior lobe is concerned with the function of gluconeogenesis. Indeed there is only one piece of direct evidence pointing to a failure of gluconeogenesis as the result of removal of the hypophysis. It has been shown that when normal rats are exposed to a low oxygen supply they appear to form new carbohydrate, apparently from protein since extra nitrogen is excreted. If however the hypophysis has been removed gluconeogenesis does not take place (Evans, G., 1936). The significance of this curious observation has not as yet been determined. This absence of definite direct evidence leads Russell (1938) to reject the hypothesis of failure of gluconeogenesis, and to adopt the view that the anterior lobe of the pituitary acts by depressing the oxidation of carbohydrate, so that in its absence there is an excess of oxidation of carbohydrate. This hypothesis provides an attractive explanation for the amelioration of pancreatic diabetes which results from hypophysectomy, and also for the sensitivity to the hypoglycaemic action of insulin and the rapid disappearance of the carbohydrate reserves in the hypophysectomized animal. However since there is as yet insufficient evidence which would enable one to determine which of these opinions is the more correct, there is little value to be obtained by pursuing the matter further in this place; it suffices for the present purpose to understand that/

that the secretion of the anterior lobe of the pituitary produces a hyperglycaemia, whether this increase in the blood sugar is due to an excess of formation of new carbohydrate or to a depression of the oxidation of carbohydrate is of no present importance.

The Action of Anterior Pituitary Extract on Human Subjects.

Although a great amount of work has been carried out on the action of extract of the anterior lobe of the pituitary on experimental animals the problem has not been studied on human subjects to any extent. Badenoch and Morris (1936) observed that the injection of anterior pituitary extract in a child suffering from coeliac disease did not produce any significant alteration in the blood sugar values up to 2 hours after the injection had been completed, but that if the blood sugar level was estimated after a period of some 12 hours had elapsed a rise in the level was apparent. They concluded that the injection of the extract produced remote rather than immediate effects. Continuing the investigation these workers were able to produce an alteration in the blood sugar curves of children suffering from coeliac disease by giving daily injections of the extract, the characteristic 'flat' curves being replaced by more normal values, and in certain instances hyperglycaemic responses being obtained. On the other hand, in 2 children convalescent from acute illnesses and not suffering from coeliac disease the injection of extract was said to produce no significant alteration in the glucose tolerance curve.

From these results and from their observations that children with coeliac/

coeliac disease were more sensitive to the hypoglycaemic action of insulin than normal children, implying that a contra-insular substance was lacking, Badenoch and Morris suggested that the anterior lobe of the pituitary played a part in the production of abnormalities of carbohydrate metabolism in coeliac disease.

The present investigation was undertaken in order to study the effects of injection of anterior pituitary extract in human subjects in view of the absence of knowledge concerning this problem.

Section Two.

The Effect of the Injection of Extract of the Anterior Lobe of the Pituitary on Carbohydrate Tolerance.

Methods. The subjects studied were patients in the wards of Professor McNee who were either convalescent from illness or in fairly good health at the time of the examination. Although they could not all be regarded as normal individuals they were in as good a state of health as might reasonably be expected among patients in general medical wards. All of them were taking ordinary ward diet and were free from any apparent disturbance of carbohydrate metabolism. A preliminary glucose tolerance curve was carried out after the ingestion of 50 grams of glucose, and thereafter anterior pituitary extract was given in quantities of one c.cm. daily for a carying number of days; at the end of this time the glucose tolerance was again estimated. Finally, after allowing a rest period of some days' duration to elapse during which no extract was given, another estimation of the glucose tolerance was made. All blood sugar curves were carried out in the morning after a 12 hours fast and about 18 hours after the last injection of anterior pituitary extract. The values were estimated by the Folin-Wu technique as modified by Herbert and Bourne (1931), all colorimetric readings being made by the author.

The particular anterior pituitary extract used was a commercial/

commercial one (Armour) of such a strength that one c.cm. was the equivalent of $\frac{1}{2}$ gram fresh gland substance. This choice of extract was made partly on account of convenience, and partly because it had already been shown to possess a delayed hyperglycaemic action in human subjects (Badenoch and Morris).

Assessment of Results. Unfortunately there is as yet no satisfactory method of comparing blood sugar curves carried out on the one individual at different times. According to some observers the peak of values should be compared while others maintain that a more satisfactory standard of comparison is provided by measuring the time taken for blood sugar to fall to a previously determined level. Both of these methods are open to criticism on the grounds of accuracy. If the peak values alone are compared then a curve with a high peak value followed by a rapid fall to a low level may be regarded as demonstrating a diminished glucose tolerance, although the rapid return to normal values would lend absolutely no support to this contention. Similarly certain curves exhibit a peak value that is not unduly high but is followed by a very slow return to the fasting level; in this instance a consideration of the peak value by itself gives no indication of the diminished sugar tolerance evidenced by the slow fall in the curve. On the other hand if the rate of fall of the curve is taken as a means of comparison then two curves with the same 2 hour readings are regarded as giving evidence of similar tolerance to carbohydrate although the intermediate values may/

may indicate comparatively wide differences in the course of the curve after the ingestion of glucose.

These difficulties in comparison that have been indicated result partly from the fact that the standard technique of assessing glucose tolerance, by taking samples of blood at intervals of half an hour for a period of 2 hours after the ingestion of glucose, provides only an imperfect indication of the changes in the blood sugar level that are actually taking place. Following the administration of a quantity of glucose the blood sugar rises to a peak which is attained, in the majority of cases, some 45 minutes later and then falls to its initial level in about 120 minutes: during this time there is a constant alteration occurring in the blood sugar level which cannot be estimated with great accuracy, unless samples are taken at intervals of five minutes of less. The standard technique adopted in this investigation of taking samples at half hour intervals means that the highest and lowest values will not be recorded unless they happen to coincide in time with that when the sample of blood is withdrawn. Accordingly a comparison of any two blood sugar curves can only be approximate.

In addition to these difficulties it is recognised that the blood sugar curve in the one individual is subject to variations which cannot always be explained. Some of these variations as will be mentioned later can be avoided by ensuring that the intake of carbohydrate in the diet is constant, and others by taking into account the presence or absence of infection. Even when these factors are well controlled glucose tolerance may still vary, and indeed/

indeed a part of the present investigation is concerned with other possible causes of these variations.

For the purposes of the present investigarion it was decided to use the highest value recorded in each glucose tolerance curve as a standard of comparison. This choice can at least be recommended on the grounds that it makes for simplicity in comparing different degrees of glucose tolerance, but it will be realized, in view of the preceding discussion, that it cannot be claimed to lead to conclusions that are invariably accurate. Nevertheless the results obtained by using this criterion for comparison are on the whole satisfactory.

Besides the establishment of a standard for comparing different blood sugar curves, it was also necessary to decide what degree of change in the peak values was required before it could be agreed that a significant alteration in glucose tolerance had occurred. For this purpose it was decided that any change in the peak value of less than 20 mg. could not be regarded as evidence of any significant alteration in the carbohydrate tolerance of the individual studied. This choice was purely arbitrary and was adopted in order to avoid, so far as was possible, any stress being placed on minor alterations in the blood sugar curves which might be observed during the course of the experiments. It should not be regarded as an admission that the extract was inactive in those cases in which only a small change in the peak value of the curve was observed, even assuming for the moment that the method of comparing the different curves was accurate in its results. In these cases it might be that too small an amount of extract was given/

given to produce any significant alteration; or it might be that too little time was allowed for any change to develop before the second sugar tolerance curve was carried out. However since there is no means of assessing the truth of these or other possibilities in any particular instance it is best that they should be regarded as showing no change which could be attributed to the action of the extract, without inferring from this that these individuals were resistant to its action.

Results. In 9 instances the variation in the glucose tolerance was negligible (less than 20 mg.); in 17 cases the result of the injection of the extract was an increase in tolerance. The remaining 8 patients responded to the extract by exhibiting a decrease in tolerance to glucose, and in this respect resembled the children suffering from coeliac disease reported by Badenoch and Morris. In this last group the effect of continuing the injections was tried in order to determine whether a temporary diabetic state could be produced in this way but, as the results demonstrate, the effect of this procedure was the disappearance of the diminished tolerance, the curves tending to return to their initial level, or a lower one. In each case a final blood sugar curve was carried out after a rest period of some days, during which time no extract was given, showed that the glucose tolerance tended to return to the level existing before the injections were given.

Table 1 summarized the results obtained in the 17 cases whose tolerance increased as the result of injection of anterior pituitary extract; in Table 2 the temporary loss of glucose tolerance/

tolerance following the use of extract is shown (8 cases); the 9 cases in whom no significant alteration could be observed are given in Table 3. In Fig. 1 the increased tolerance to glucose following the injection of extract is shown graphically, while Fig. 2 shows in the same way the loss of glucose tolerance that occurred in the second group. Fig. 3 demonstrates that this loss of tolerance was temporary in nature and disappeared when the injections were continued.

Discussion. Two effects were noted as the result of injection of anterior pituitary extract; in the larger group a gain in carbohydrate tolerance was observed and in the smaller a ~~gain~~ in tolerance. It is necessary to find an explanation for these results and it is reasonable first to enquire whether there was any apparent difference in those individuals who gained in tolerance after extract, as compared with those who lost tolerance. It can hardly be denied that the age of the individual who was examined in this way is likely to be a factor of importance in deciding the nature of the response, but in order to determine whether any relationship existed between the age of the patient and the type of response elicited it would be necessary to examine a large number of individuals, much larger than the present series, therefore this question cannot be considered at the present time, important though it may be. The number of subjects in this part of the investigation is too small to permit of any further subdivision of the results, and so, in addition to the question of the age/

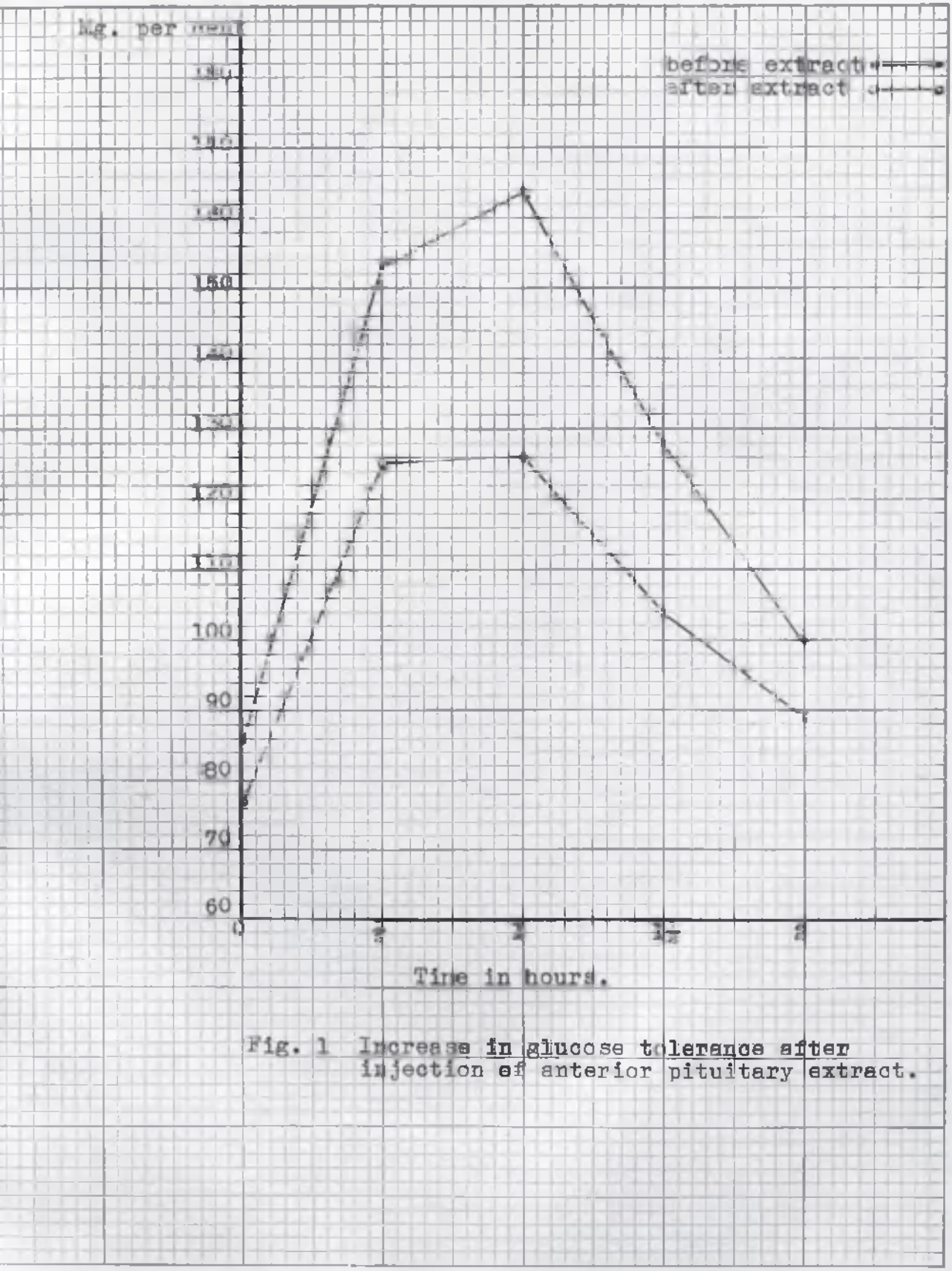

Fig. 1 Increase in glucose tolerance after injection of anterior pituitary extract.

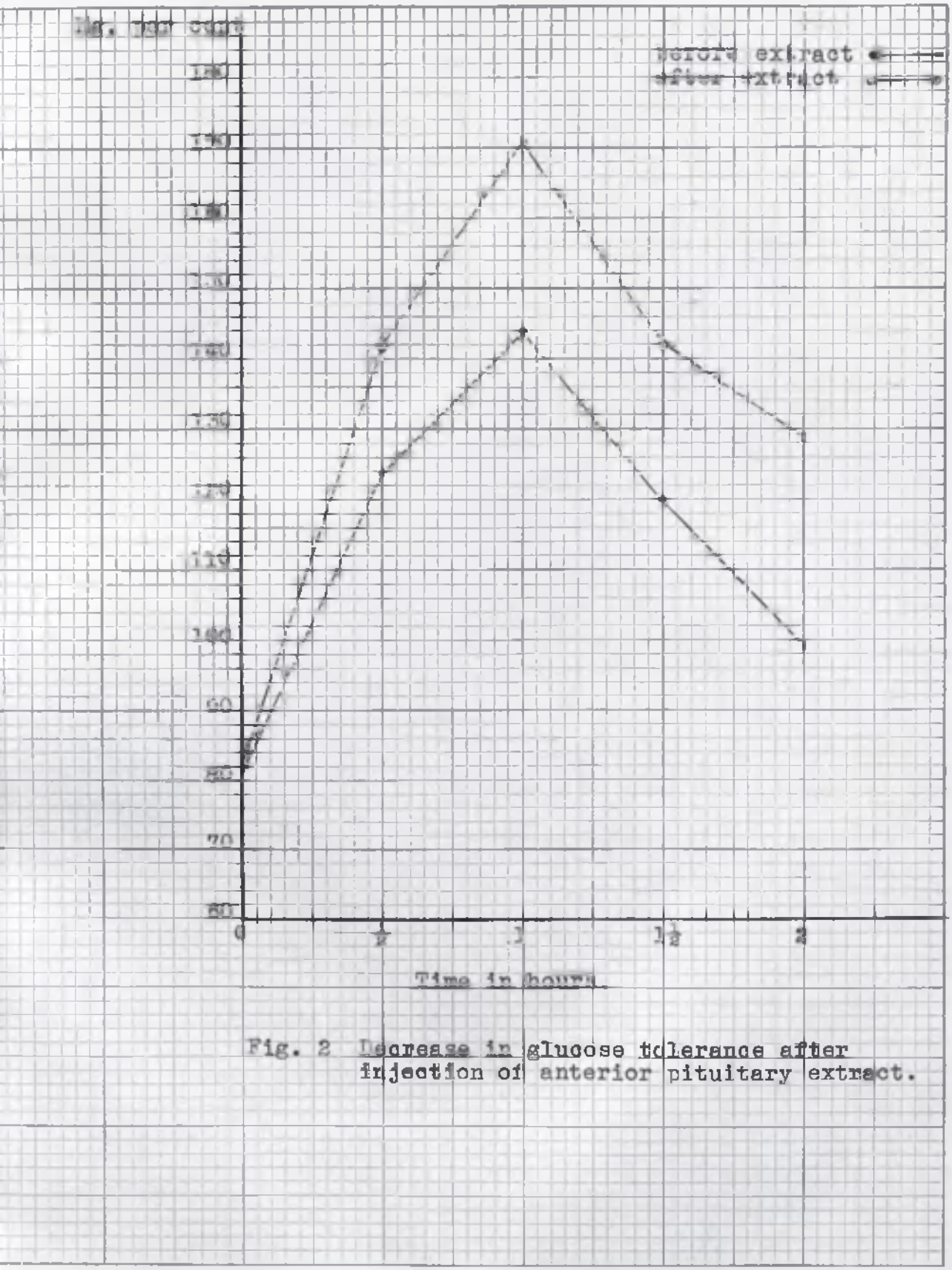

Fig. 2 Decrease in glucose tolerance after injection of anterior pituitary extract.

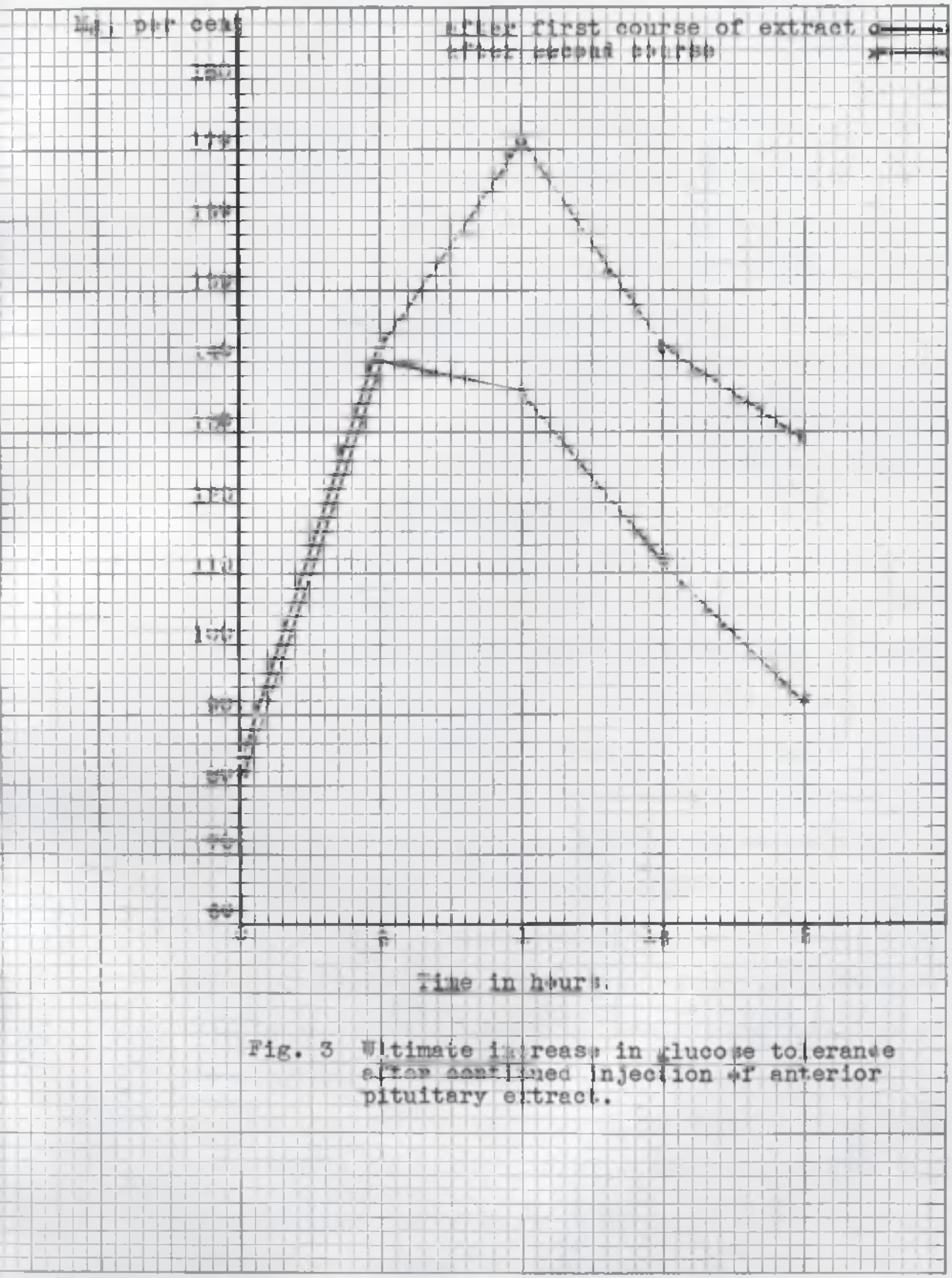

Fig. 3 Ultimate increase in glucose tolerance after continued injection of anterior pituitary extract.

age of the patient, that of the sex must also be passed over without inferring that it is of no importance in determining the nature of the response to anterior pituitary extract. Another factor which might well be of importance, but which cannot be considered in this place for the same reason, is the nature of the disease which originally required the admission of the patient to hospital. This factor might indeed be regarded as of prime importance in deciding the response of the subject, but since the subjects chosen for study were those who could reasonably be regarded as being in fairly good health at the time of the examination, it is considered that its influence was reduced to a minimum.

At this stage of the investigation there was no attempt to standardise the dose of extract given to each subject and so the curves obtained represent the effects of widely different amounts of anterior pituitary extract; the influence of the dosage of extract injected must therefore be considered. At first sight there is no apparent relationship between the total quantity of extract administered and the nature of the response exhibited by the subject, the same dose producing different responses in different patients, and a small dose which was capable of producing an increase in glucose tolerance in one case might produce a reduction in tolerance in another. However since those subjects who responded initially by losing tolerance were subjected to continued treatment with extract until they began to regain their former degree of tolerance to sugar, it comes about that the larger amounts used all resulted in the production of an increase in carbohydrate tolerance. Consideration of this point does not however/

however shed any light on the factors responsible for the existence of two types of response.

In examining the blood sugar curves obtained before the administration of extract a difference is evident between those individuals who gained tolerance and those who lost. Of the 17 subjects who gained tolerance after the administration of the extract, 16 had peak values of more than 150 mg.; of those 8 cases who lost tolerance after the extract was given 5 had peak values of less than 150 mg. This difference seemed sufficiently striking to warrant some investigation, and further interest was aroused when it was noticed that 3 of the patients who developed diminished carbohydrate tolerance as the result of the injections had 'flat' curves to begin with, that is to say that the blood sugar level did not rise more than 40 mg. after taking 50 gm. of glucose (Cases 19, 20, and 21). The belief that this observation might prove to be of importance was strengthened by considering the work of Badenoch and Morris who noted that the injection of anterior pituitary extract in cases of coeliac disease, in which condition a 'flat' blood sugar curve is a characteristic finding, always resulted in a diminution in carbohydrate tolerance. It is generally regarded that in healthy individuals the peak value of the blood sugar curve is related to the carbohydrate intake, and so it became necessary to determine whether there was any relationship between the nature of the response to anterior pituitary extract and the quantity of dietary carbohydrate. This problem was examined in some detail and will be considered in a later section.

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This difference was the only one discovered between the 2 groups of cases apart from those of age, sex and disease which have already been mentioned, and accordingly attention was directed to the extract itself in an attempt to find an explanation for the existence of the 2 types of response.

Two properties have been attributed to the anterior pituitary in considering its action on carbohydrate metabolism, first a 'diabetogenic' action producing a diminution in glucose tolerance, and second an insulin stimulating or 'pancreotropic' action causing a gain in sugar tolerance.

The ultimate gain in carbohydrate tolerance which was observed to follow the injection of the anterior pituitary extract in all cases might well be attributed to a 'pancreotropic' or insulin stimulating action, but it is impossible to explain the temporary loss of tolerance which was a feature in certain instances on this basis, unless it is supposed that both factors were present in the extract and exerted their effects at different times. For example, if to begin with the blood sugar raising, or 'diabetogenic', action was the dominant action in causing an initial loss of glucose tolerance, transitory in its effect so that in the majority of instances this property could be demonstrated only in certain cases, and then the insulin stimulating action came into play, abolishing the previous hyperglycaemia and causing a fall in the blood sugar values. That this is a possible explanation cannot be denied but the complicated nature of the hypothesis renders it unattractive if a simpler one can be obtained. Nevertheless it cannot/

cannot be disproved definitely without taking into account results obtained later in the investigation.

Another simpler explanation presents itself. If it is assumed that the extract possesses only a hyperglycaemic action, and indeed the only evidence that a pancreotropic action exists is that advanced by Anselmino and Hoffman which is by no means universally accepted, then the increase in glucose tolerance may be assigned to a compensatory response on the part of the pancreas. In certain individuals this compensatory reaction is delayed so that tolerance is lost to begin with before the pancreas has time to respond. If this view is accepted then all that remains to be explained is why certain individuals are slow in compensating for the hyperglycaemia following the injection of the extract.

The question of which of these hypotheses was the correct one could not be established by continuing the study of the effect of injecting the extract as described in the present section, but it was felt that indirect evidence might be obtained that would assist in providing the answer. No endocrine gland other than the anterior pituitary has been credited with producing a secretion with a pancreotropic action, whereas the property of producing a hyperglycaemia is not confined to the anterior pituitary. If the effects of injection of hyperglycaemic extracts obtained from other glands were similar to those obtained with the anterior pituitary then it might reasonably be assumed that the results were due to the hyperglycaemia, and not to any hormone producing a secretion of insulin by acting directly on the islet tissue of the pancreas.

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In order to test this supposition the action of extract of the posterior lobe of the pituitary was studied in a number of individuals.

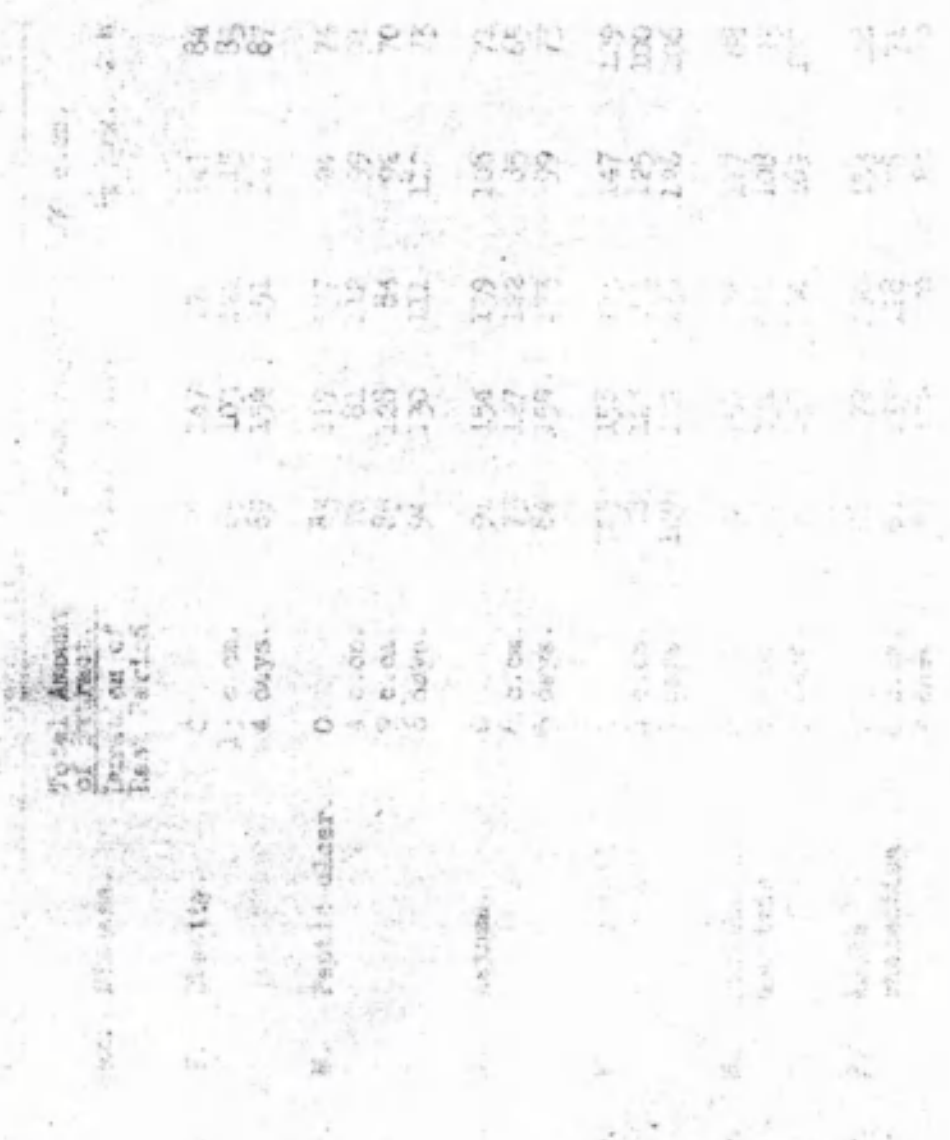

Table 1.

Increase in Glucose Tolerance after the Injection of Anterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c.cm.
1	40 yr.	F.	Obesity.	0	75	147	172	141	84	-50
				13 c.cm.	63	103	122	115	83	
				4 days.	69	159	151	147	87	
2	39 yr.	M.	Peptic ulcer.	0	83	119	137	94	74	-25
				4 c.cm.	76	81	112	99	91	
				9 c.cm.	85	128	84	92	70	
				6 days.	94	130	111	112	73	
3.	62 yr.	M.	Asthma.	0	91	154	139	108	71	
				6 c.cm.	73	127	122	85	65	-27
				5 days.	84	159	133	99	73	
4.	43 yr.	F.	Rheumatoid arthritis.	0	105	158	175	147	129	
				6 c.cm.	78	128	151	125	100	-24
				7 days.	109	122	136	126	106	
5.	43 yr.	M.	Peripheral neuritis.	0	94	158	178	117	88	
				8 c.cm.	78	131	151	108	93	-27
				5 days.	76	135	164	169	107	
6.	15 yr.	F.	Acute rheumatism.	0	86	172	196	153	118	
				6 c.cm.	69	133	118	98	71	-63
				3 days.	82	122	130	89	79	

Table 1. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c.cm.
7.	58 yr.	F.	Fibrositis.	0	93	133	188	182	118	
				6 c.cm.	85	130	131	137	130	-51
				14 c.cm.	82	122	130	89	79	
				2 days.	82	111	112	115	106	
8.	47 yr.	F.	Rheumatoid arthritis.	0	85	179	192	164	139	
				10 c.cm.	86	131	113	125	125	-61
				5 days.	78	102	156	158	107	
9.	31 yr.	F.	Anxiety neurosis.	0	94	156	185	132	101	
				8 c.cm.	78	164	149	122	95	-21
				5 days.	82	175	153	114	111	
10.	38 yr.	F.	Headache.	0	72	124	158	106	90	
				13 c.cm.	70	105	112	72	80	-46
				4 days.	78	126	134	95	85	
11.	16 yr.	F.	Chorea.	0	87	173	130	114	108	
				13 c.cm.	80	135	107	95	88	-38
				5 days.	91	128	120	108	85	
12.	18 yr.	M.	Acute rheumatism.	0	82	184	170	122	88	
				6 c.cm.	74	131	144	104	76	-40
				5 days.	87	154	166	109	84	
13.	40 yr.	F.	Rheumatoid arthritis.	0	81	140	151	125	94	
				11 c.cm.	74	125	114	88	70	-26
				10 days.	76	152	127	120	90	

Table 1. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c.cm.
14.	41 yr.	M.	Influenza.	0	88	164	127	85	99	
				6 c.cm.	85	128	93	80	74	-36
				6 days.	83	156	102	76	88	
15.	47 yr.	M.	Rheumatoid arthritis.	0	84	140	162	119	108	
				6 c.cm.	82	127	131	96	86	-31
				5 days.	89	116	136	101	88	
16.	44 yr.	F.	Neurasthenia.	0	88	146	159	126	98	
				6 c.cm.	82	127	131	96	86	-28
				8 days.	86	138	154	124	88	
17.	39 yr,	M.	Peptic ulcer.	0	76	149	164	138	96	
				7 c.cm.	81	112	134	121	108	-30
				3 days.	88	135	138	120	84	
Mean:					86	153	164	128	100	
					77	125	126	104	89	
					84	137	137	117	91	

Table 2.

Decrease in Glucose Tolerance after the Injection of Anterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract, Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mg./100 c.cm.
18.	21 yr.	M.	Acute rheumatism.	0	78	102	139	120	83	
				9 c.cm.	81	147	161	118	91	+22
				17 c.cm.	72	145	93	78	67	
				7 days.	74	83	98	89	81	
19.	38 yr.	F.	Peptic ulcer.	0	78	101	116	105	76	
				4 c.cm.	83	154	200	156	108	+84
				16 c.cm.	85	176	138	110	88	
				5 days.	83	114	149	132	86	
20.	33 yr.	M.	Peptic ulcer.	0	80	105	115	90	95	
				5 c.cm.	75	137	133	74	81	+22
				12 c.cm.	88	130	154	118	80	
				18 c.cm.	82	125	120	98	90	
				4 days.	80	128	140	90	85	
21.	29 yr.	F.	Acute rheumatism.	0	87	125	127	125	115	
				6 c.cm.	93	130	149	145	145	+22
				10 c.cm.	103	125	143	130	119	
				18 c.cm.	94	121	137	118	98	
				4 days.	82	147	151	98	85	
22.	44 yr.	F.	Haematemesis.	0	96	141	172	145	121	
				7 c.cm.	81	149	216	166	161	+44
				19 c.cm.	84	156	166	137	116	
				6 days.	84	143	170	114	81	

Table 2. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mg./100 c.cm.
23.	69 yr.	F,	Pernicious anaemia.	0	75	142	167	139	95	
				6 c.cm.	76	141	132	189	161	+22
				12 c.cm.	79	149	178	147	134	
				19 c.cm.	80	176	179	121	103	
				26 c.cm.	81	156	151	118	74	
24.	52 yr.	M.	Peptic ulcer.	0	88	156	166	111	102	
				6 c.cm.	79	112	222	156	154	+56
				12 c.cm.	80	140	158	123	96	
				6 days.	76	178	174	129	98	
25.	48 yr.	F.	Rheumatoid arthritis.	0	76	111	147	125	102	
				10 c.cm.	103	169	157	129	129	+22
				15 c.cm.	81	110	126	112	109	
				5 days.	77	107	123	122	111	
Mean:					82	124	144	120	99	
					84	142	171	142	129	
					82	140	136	112	92	

Table 3.

No Significant Alteration in Glucose Tolerance after the Injection of Anterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
26.	43 yr.	F.	Peptic ulcer.	0	72	114	122	105	91	
				13 c.cm.	69	106	112	70	70	-10
				4 days.	83	125	111	94	84	
27.	29 yr.	M.	Peptic ulcer.	0	81	120	131	95	84	
				11 c.cm.	63	127	139	88	69	+8
				10 days.	74	151	128	118	90	
28.	24 yr.	M.	Peptic ulcer.	0	88	154	97	56	73	
				4 c.cm.	85	164	73	85	99	+10
				6 days.	83	154	90	61	90	
29.	40 yr.	M.	Herpes Zoster.	0	92	182	169	120	90	
				3 c.cm.	74	181	154	105	79	-1
				4 days.	87	156	166	104	83	
30.	23 yr.	M.	Peptic ulcer.	0	85	130	143	118	109	
				6 c.cm.	86	119	143	111	79	nil.
31.	18 yr.	F.	Acute rheumatism.	0	117	153	122	112	106	
				13 c.cm.	80	135	117	94	91	-18
				5 days.	91	128	120	95	85	
32.	40 yr.	F.	Neurasthenia.	0	90	159	147	96	100	
				6 c.cm.	82	147	151	98	85	-8
				8 days.	86	139	164	133	88	

Table 3. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
33.	30 yr.	M.	Peptic ulcer.	0	72	136	139	115	65	
				7 c.cm.	76	128	132	106	82	-7
				6 days.	70	128	112	109	85	
34.	36 yr.	M.	Peptic ulcer.	0	78	154	151	98	68	
				7 c.cm.	83	112	134	123	96	-17
Mean:					86	145	136	102	87	
					78	136	128	98	83	

Section Three.

The Influence of the Posterior Lobe of the Pituitary on Carbohydrate Metabolism.

The Action of Posterior Pituitary Extract on the Blood Sugar Level. There has been a considerable lack of agreement concerning the effect of injection of extract of the posterior lobe of the pituitary on the blood sugar level. It is usually considered that the result is the production of a hyperglycaemia but experimental findings do not invariably justify this assumption. Burn (1923) and Clark (1925) concluded that following the injection of posterior pituitary extract there was usually a rise in the blood sugar level although occasionally the hyperglycaemia might be negligible in degree, and in a few instances the blood sugar instead of rising was observed to fall. Later observers have all tended to emphasize that hyperglycaemia is the result most commonly found, and have made little or no reference to the occasional absence of hyperglycaemia noted by the earlier workers so that the occurrence of the latter type of response has apparently been largely forgotten. Cohen and Libman (1936) investigated the effect produced in the blood sugar level of man by the injection of posterior pituitary extract and obtained results differing sharply from those obtained in the case of experimental animals. These workers observed that subcutaneous injection of the extract

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in therapeutic doses had no appreciable influence on the blood sugar level. It is most probable that the reason for this apparent contradiction of previous findings depends on the differences in the relative quantities of the extract used, the effects produced by injecting $\frac{1}{2}$ c.cm. of extract into a small animal, such as a rabbit, obviously cannot be directly compared with those obtained after the injection of the same quantity into a human subject. Therefore in view of the careful work of Cohen and Libman it can be concluded that the injection of posterior pituitary extract in small doses does not cause any appreciable alteration in the blood sugar level in man. This conclusion does not imply that extract of the posterior lobe of the pituitary is without any influence on carbohydrate metabolism. For example, it has been shown both experimentally and clinically that posterior pituitary extract is antagonistic to the action of insulin, but the consideration of this action must be deferred until the mode of action of the extract on carbohydrate metabolism is considered.

The Mode of Action of Extract of the Posterior Lobe of Pituitary on Carbohydrate Metabolism. There is a similar lack of agreement concerning the mode of action of posterior pituitary extract on the metabolism of carbohydrate and many hypotheses have been advanced, some of which cannot be considered as affording a satisfactory explanation of the experimental findings. The observations of Burn (1923) that posterior pituitary extract was capable of diminishing or abolishing the hypoglycaemic action of insulin and that the rise in the blood sugar level that occurred

in the rabbit, which was the animal studied, after the injection of the extract was insufficient in itself to explain this result, stimulated a considerable volume of interest. Lawrence and Hewlet (1925) suggested that the antagonism of insulin was produced by the mobilization of sugar from the liver or muscles or both, and further suggested that this mobilization of sugar was the result of a stimulation of the sympathetic nervous system since the administration of ergotamine prevented the action. Nitescu (1928) and Clark (1926) were unable to confirm that ergotamine prevented this action of posterior pituitary extract, and the latter was able to produce a telling argument against the acceptance of the hypothesis advanced by Lawrence and Hewlet. This worker pointed out that since posterior pituitary extract had been found to inhibit the hyperglycaemia that normally followed the injection of adrenalin (Burn, 1923), it was unlikely to antagonise insulin by provoking a secretion of adrenalin which was itself antagonised by extract of the posterior lobe.

Clark (1928) concluded from experiments on cats, in which the liver had been excluded from the circulation, that the source of the hyperglycaemia observed to follow the injection of posterior pituitary extract in the intact animal was the glycogen stores of the liver. Furthermore, evidence was advanced to show that this action on the liver carbohydrate was not caused through the sympathetic nervous system, either by direct stimulation or by means of the adrenal glands. It is curious that this worker did not attempt to explain why, if this was the mode of action of extract/

extract of the posterior pituitary, the antagonism of insulin could not be explained on the basis of a hyperglycaemia following the injection of the extract of the posterior lobe.

Some reference has already been made to the work of Cohen and Libman which is of especial interest in the present investigation as it deals with the effects of injection of posterior pituitary extract in the human subject. It will be remembered that these workers found subcutaneous injection of extract of the posterior lobe of the pituitary to have no appreciable influence on the level of the blood sugar, and thus far confirmed the work of Burn, and of Lawrence and Hewlet, in producing no evidence of the direct mobilization of glucose by its action. (Cohen and Libman, 1936). This study has been carried a step further (Cohen and Libman, 1937) in order to discover the explanation of the antagonism to insulin shown by posterior pituitary extract, an antagonism which cannot be explained on the grounds of the production of a hyperglycaemia. For this purpose these workers compared the effect of the administration of glucose on the blood sugar level of healthy male subjects with that observed when posterior pituitary extract was given at the same time as the glucose. It was observed that in certain individuals the combined administration of glucose and posterior pituitary extract resulted in a much greater rise in the blood sugar than that occurring after the administration of glucose alone. In those cases where this finding was noted it would be shown that the combined administration of glucose and extract resulted in a diminution of the difference between the arterial and venous blood sugar levels, in comparison

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with the difference observed when glucose alone was given. That is to say, posterior pituitary extract was capable of decreasing the arterio-venous blood sugar difference. Now, ever since the existence of this difference between the arterial and venous blood sugar levels occurring after the ingestion of glucose was first demonstrated by Foster (1922), it has been assumed that it represents the activity of the tissues in taking up glucose from the arterial blood stream and therefore serves as an index of insulin activity. On these grounds Cohen and Libman conclude that extract of the posterior lobe of the pituitary antagonises insulin by inhibiting its peripheral action. In this way the antagonism to the hypoglycaemic action of insulin by posterior pituitary extract can be understood, even when it is appreciated that injection of the extract does not invariably result in a hyperglycaemia. It is also possible to understand, as the result of this work of Cohen and Libman, why the relatively large doses used in experimental animals may raise the blood sugar level to considerable heights by obliterating the activity of the circulating insulin, while a therapeutic dose in man does not result in hyperglycaemia but may still be capable of antagonizing the action of insulin.

Apart from the studies mentioned in the preceding paragraphs, and a number of investigations merely confirming the fact that injection of extract of the posterior lobe of the pituitary is capable of producing a rise in the blood sugar level of experimental animals, the action of the extract has not been so carefully nor so enthusiastically investigated as is the case with extract

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of the anterior lobe of the same gland. Indeed, since the findings of the Houssay school first began to excite interest, the attention of the experimental physiologists in the field of carbohydrate metabolism has been almost wholly directed towards the anterior lobe of the pituitary with resulting neglect of the posterior lobe and in its actions. From time to time however references to the action of the posterior lobe on the metabolism of carbohydrate crop up in the mass of experimental data collected concerning the anterior lobe. As is common in this field of experimental physiology it is not difficult to collect observations which are entirely contradictory.

Geiling, Campbell and Ishikawa (1927) were amongst the earliest observers to discover that removal of the hypophysis in experimental animals resulted in a state of hypersensitivity to the hypoglycaemic action of insulin. Possibly being influenced by the fashion of the moment they concluded that this hypersensitivity was due to the absence of the posterior lobe, and that removal of the anterior lobe alone did not have this effect, whereas if the secretion of the posterior lobe was absent or diminished as the result of experimental damage the activity of insulin was greatly exaggerated. This finding that it is the loss of the posterior lobe in hypophysectomy, and not the loss of the anterior lobe, that produces the insulin hypersensitivity is directly opposed to the conclusions reached by all later investigators in this field, who are unanimous in declaring that it is the absence of the anterior lobe that is chiefly responsible for the production of the hypersensitivity to the hypoglycaemic action of insulin exhibited/

exhibited by the hypophysectomized animal. It is therefore reasonable to conclude that the posterior lobe is not of primary importance in the production of this phenomenon but whether it is of minor importance is not certain. In a recent investigation Pencharz, Cori and Russell (1936) concluded that removal of the posterior lobe alone did not increase the sensitivity of the animal to the action of insulin.

The relation of the posterior lobe to another of the characteristics of the hypophysectomized animal, the rapid fall in the carbohydrate levels of body following the completion of the operation, has been studied to some extent. Geiling and others (1927) observed that extract of the posterior lobe was capable of preventing the onset of hypoglycaemia in the hypophysectomized animal. Houssay and di Benedetto (1932) found that implantation of the posterior lobe in the hypophysectomized toad tended to restore tha animal to normal, although its action in this respect was much weaker than that observed when the anterior lobe was implanted. Similarly Houssay, Benedetto and Mazzocco (1933) noted that injection of posterior pituitary extract resembled anterior pituitary extract in its power of preventing the fall in the carbohydrate stores of the body which normally occurred after hypophysectomy in the toad but differed from it in being less effective. An observation contrary to this last is that of Russell and Bennett (1937) who were of the opinion that absence of the posterior lobe did not account in any way for the fall in carbohydrate levels following removal of the/

the hypophysis.

The only investigation into the 'diabetogenic' properties of posterior pituitary extract is that of Houssay and Biasotti (1931b) who assayed the 'diabetogenic' powers of extracts of many tissues of the body. According to this report extracts of the heart, pancreas, and adrenals had no such activity; extracts obtained from the kidney, lung, muscle, thyroid, and ovary had practically no activity; the placenta provided an extract with a slight but inconstant action; the anterior lobe of the pituitary gave an extract which was active, while the posterior lobe was also active but to a lesser extent.

In the face of such contradictory findings as have been quoted in this section, it is difficult to decide whether there is convincing evidence that the posterior lobe of the pituitary plays a part of any importance in the metabolism of carbohydrate, and the decision is not made any easier when it is appreciated that the study of its action is to a large extent being neglected at the present time. It can be taken as certain that the dominant role is played by the anterior lobe, but does the posterior lobe play any part at all? In view of the observations of Houssay and his colleagues, and taking into account their familiarity with the activity of extracts of the anterior lobe and their great experience in this field of experimental physiology, it is probable that extracts of the posterior lobe of the pituitary have a similar though weaker action to that of the anterior, at least in some respects. More than this cannot be said.

Section Four.

The Effect of the Injection of Extract of the Posterior Lobe of the Pituitary on Carbohydrate Tolerance.

Methods. The patients for study were selected in the same manner as has been previously outlined, and resembled the others as regards their general condition and dietary intake. The examination was proceeded with in the same way, glucose tolerance curves being carried out before and after the course of injections, and again after a rest period. The particular extract of the posterior lobe of the pituitary used was a commercial one (Allen and Hanbury) of such a strength that one c.cm. contained 10 pressor units: the total quantities of extract injected in each case varied from 1.5 c.cm. to 13 c.cm. and was given in daily injections of 0.5 c.cm.

Results. As in the previous experiments an alteration of at least 20 mg. was required in the peak value of the blood sugar curve before any change observed was regarded as being of significance. A total number of 21 individuals were studied in this way: judged on the standard described there was only a negligible variation in the glucose tolerance in 8 instances; improvement was noted in 8 cases and the remaining 5 patients exhibited some decrease in carbohydrate tolerance. In this last group, as with those subjects given anterior pituitary extract, the effect of continuing/

continuing the injections was tried with a similar result, tolerance being more or less regained. Case 45 was an exception to this rule as there was insufficient time available in which to continue the injections until some recovery of carbohydrate tolerance appeared. There is however no reason to believe that had the injections been continued any other result would ultimately have been secured, accordingly this case is classified among those showing a temporary failure of glucose tolerance as the result of the injection of posterior pituitary extract. In connection with these results it should be emphasised that although no significant alteration could be demonstrated in 8 cases according to the criterion adopted, there is no intention to maintain that these particular individuals were entirely uninfluenced by the action of the extract. On this point reference may be made to the comment on the results obtained with anterior pituitary extract.

Table 4 shows the increase in glucose tolerance that occurred following the injection of posterior pituitary extract; in Table 5 the temporary loss of tolerance that occurred in certain cases is shown, while Table 6 illustrates the negligible alteration in tolerance which was all that could be demonstrated in the remainder. In Fig. 4 the increased tolerance following the injection of the extract is shown graphically; Fig. 5 illustrates the loss of tolerance in certain cases under the same conditions and Fig. 6 demonstrates that this loss was only of a temporary nature and disappeared/

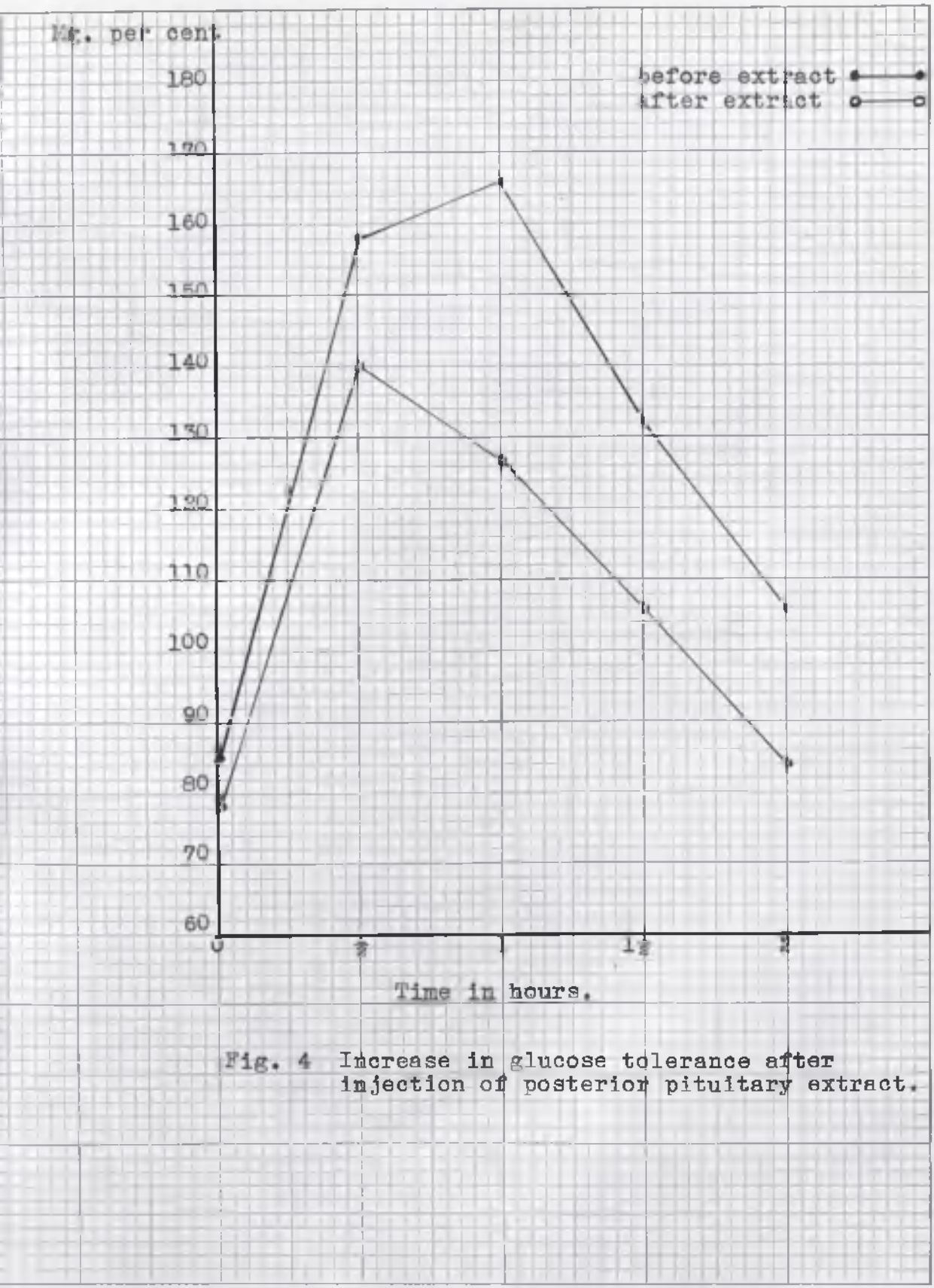

Fig. 4 Increase in glucose tolerance after injection of posterior pituitary extract.

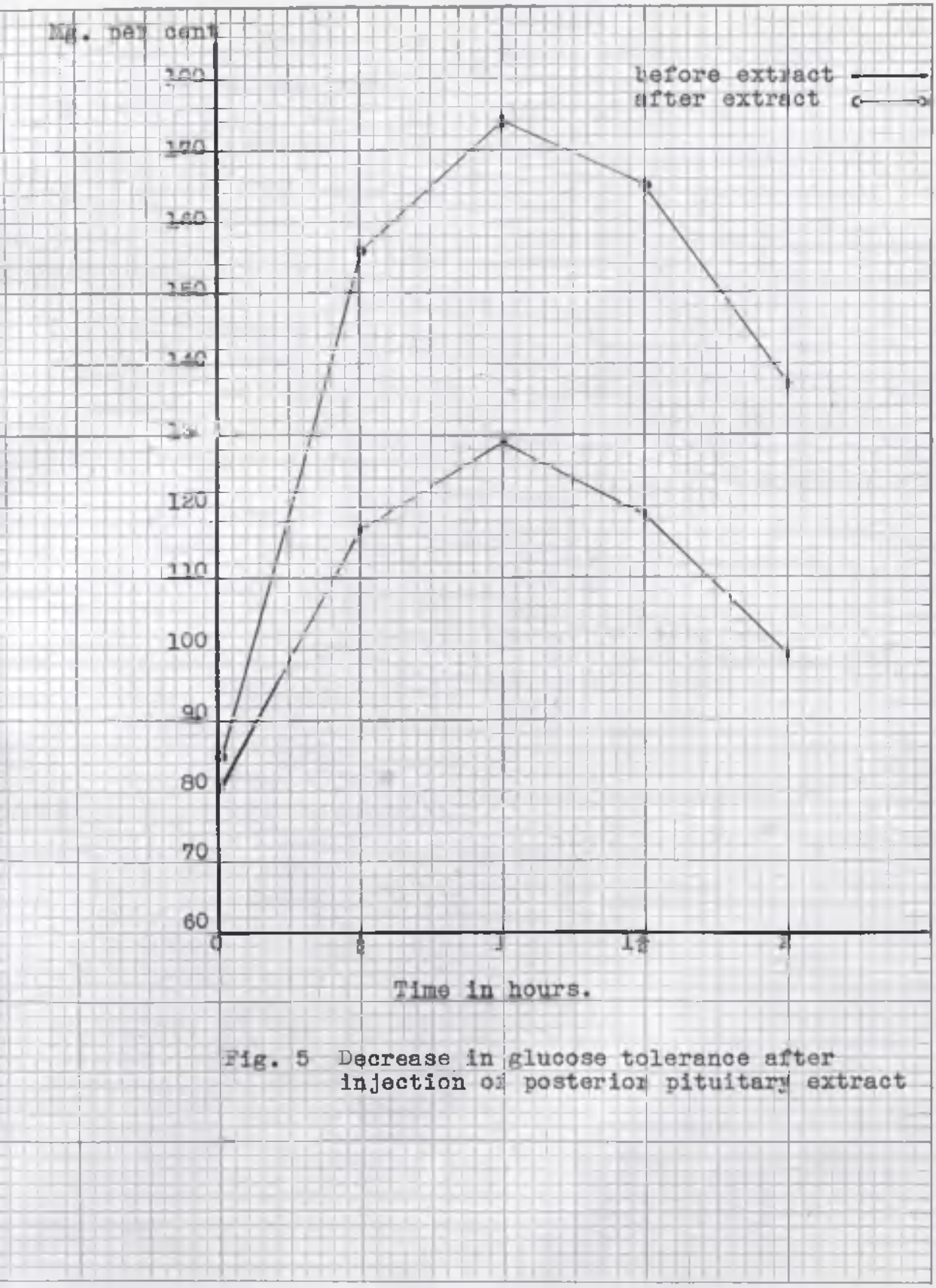

Fig. 5 Decrease in glucose tolerance after injection of posterior pituitary extract

Fig. 6 Ultimate increase in glucose tolerance after continued injection of posterior pituitary extract.

disappeared when the injections were continued.

Discussion. There is a striking resemblance between the results obtained after the injection of posterior pituitary extract to those secured when anterior pituitary extract was used. In both cases the larger group responded to the injections by showing some gain in carbohydrate tolerance, and in both cases there was a smaller group who lost tolerance to begin with, but tended to regain it when the administration of the extract was continued. This resemblance between the effects of the 2 different extracts suggests some similarity in their mode of action and this point will be discussed at some length later.

As was the case when anterior pituitary extract was used the smallness of the numbers examined does not permit of any subdivision of the cases in an attempt to investigate whether there are any inherent differences in the subjects themselves to explain the existence of two types of response. The same difference in the peak values of the blood sugar curves of the 2 groups was however observed, as was the case when anterior pituitary extract was used. Of the 8 subjects who gained in tolerance all had peak values of more than 150 mg.; of those who lost tolerance 3 out of 5 had peak values of less than 150 mg. This finding strengthens the belief that there exists a connection between the height of the blood sugar curve and the nature of the response to pituitary extracts and will be the subject of comment in a later section. In the meantime attention will be directed towards

the similarity in the results obtained with extracts of both the anterior and posterior lobes of the pituitary, and this will be studied in order to determine whether the finding sheds any light on the mode of action of pituitary extracts on carbohydrate tolerance.

Table 4.

Increase in Glucose Tolerance after the Injection of Posterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c.cm.
35.	17 yr.	F.	Simple goitre.	0	78	178	147	133	95	
				12 c.cm.	82	147	138	122	108	-31
				5 days.	81	103	113	101	86	
36.	14 yr.	M.	Acute rheumatism.	0	111	172	163	156	128	
				10 c.cm.	84	174	101	138	86	-62
				5 days.	91	169	217	158	191	
37.	13 yr.	M.	Chorea	0	84	172	122	111	100	
				10 c.cm.	79	147	90	80	61	-25
				9 days.	87	124	100	97	90	
38.	18 yr.	F.	Pleurisy.	0	78	130	156	149	117	
				9 c.cm.	79	114	129	133	113	-25
				7 days.	78	116	97	83	92	
39.	42 yr.	F.	Neurasthenia.	0	86	158	144	138	109	
				12 c.cm.	81	127	130	108	89	-28
				5 days.	82	129	138	121	103	
40.	14 yr.	F.	Chorea.	0	79	160	177	124	98	
				10 c.cm.	70	143	136	105	87	-34
				5 days.	75	149	166	131	92	
41.	30 yr.	F.	Normal.	0	85	162	143	118	101	
				15 c.cm.	73	132	96	80	62	-30
				4 days.	78	129	133	117	98	

Table 4. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c.cm.
42.	38 yr.	F.	Anaemia.	0	80	132	176	124	99	
				10 c.cm.	78	138	98	86	67	-36
				5 days.	86	126	121	108	86	
Mean:					85	158	166	132	106	
					78	140	127	106	84	
					82	131	136	114	96	

Table 5.

Decrease in Glucose Tolerance after the Injection of Posterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mg./100 c.cm.
43.	32 yr.	F.	Anaemia.	0	87	133	149	153	121	
				10 c.cm.	114	181	190	204	151	+51
				20 c.cm.	118	165	171	181	134	
				5 days.	105	137	178	133	120	
44.	27 yr.	M.	Acute rheumatism.	0	70	122	143	139	128	
				4 c.cm.	68	132	181	166	152	+38
				12 c.cm.	75	130	147	128	98	
				4 days.	80	136	154	140	107	
45.	47 yr.	F.	Pyuria.	0	85	192	107	92	73	
				6 c.cm.	84	128	137	128	133	
				12 c.cm.	85	200	232	192	181	+40
				7 days.	75	128	160	137	113	
46.	27 yr.	F.	Anxiety Neurosis.	0	70	110	129	114	91	
				12 c.cm.	76	131	158	122	80	+29
				17 c.cm.	72	140	126	95	101	
				5 days.	77	134	115	105	90	
47.	47 yr.	M.	Peptic ulcer.	0	86	126	118	96	84	
				4 c.cm.	84	137	169	142	120	+43
				10 c.cm.	78	128	139	123	110	
				4 days.	83	159	108	98	75	

Table 5. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mg./100 c.cm.
Mean:					80	117	129	119	99	
					85	156	174	165	137	
					83	141	146	132	111	

Table 6.

No Significant Alteration in Glucose Tolerance after the Injection of Posterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
48.	13 yr.	M.	Acute nephritis.	0	78	113	91	84	90	
				12 c.cm.	75	88	99	62	69	-14
				5 days.	81	119	87	92	89	
49.	47 yr.	F.	Rheumatoid arthritis.	0	64	111	133	113	93	
				12 c.cm.	73	125	147	121	79	+14
				5 days.	78	131	117	111	92	
50.	42 yr.	F.	Obesity.	0	87	149	133	133	119	
				10 c.cm.	86	128	135	121	107	-14
				5 days.	86	126	122	109	97	
51.	40 yr.	F.	Neuralgia.	0	91	158	175	120	113	
				10 c.cm.	72	124	166	111	92	-9
				5 days.	84	163	166	115	100	
52.	31 yr.	M.	Peptic ulcer.	0	84	128	122	101	89	
				2 c.cm.	82	128	128	109	75	nil.
				4 days.	81	159	109	98	75	
53.	56 yr.	F.	Pernicious anaemia.	0	83	132	130	102	89	
				2 c.cm.	78	128	133	132	94	+1
				4 days.	86	143	147	128	87	
54.	22 yr.	F.	Vaginitis.	0	71	106	122	83	75	
				4 c.cm.	68	115	139	85	89	+17
				4 days.	70	110	130	101	64	

Table 6. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall mg./100 c.cm.
55.	26 yr.	F.	Acute rheumatism.	0	84	142	101	70	80	
				10 c.cm.	72	133	93	72	56	-9
				9 days.	76	140	122	80	80	
Mean:					80	130	126	101	94	
					76	121	130	102	83	
					80	136	125	104	88	

Section Five.

The Action of Extracts of the Anterior and Posterior Lobes of the Pituitary on Glucose Tolerance.

The object in extending this investigation to cover the effect of extract of the posterior lobe of the pituitary on tolerance to glucose was, as has been previously outlined, to determine whether the results obtained might help in deciding the mechanism of action of extracts obtained from the anterior lobe. It was hoped that any similarity of action which might exist between the two extracts might be of value in carrying the discussion further. It is considered that the results which have been enumerated are sufficiently striking to enable certain conclusions to be made at this stage of the investigation. It has been pointed out that the results obtained by injecting anterior pituitary extract might be explained by assuming the presence of 'pancreotropic' and 'diabetogenic' properties in the extract, or by assuming that the different results were occasioned by a variation in the response of each individual to the hyperglycaemic properties of the extract. In view of the fact that posterior pituitary extract has never been credited with the power of directly stimulating the secretion of insulin, but has universally been regarded as possessing contra-insular properties, and/

and since it has been demonstrated in the present investigation that the effects produced by the administration of the extract of the posterior lobe are similar to those obtained when anterior lobe extract is used, it is concluded that the alteration in glucose tolerance is the result of the contra-insular actions of the extracts and not of any direct stimulation of the islets of Langerhans. That is to say that the improvement in glucose tolerance is to be attributed to a compensatory response, on the part of the subject, to the hyperglycaemic actions of the extracts, and the temporary diminution in tolerance noted in certain instances may be regarded as being due to a lag in the compensatory reaction.

In the case of the anterior lobe of the pituitary there is a considerable volume of evidence based on animal experimentation in support of this view. Baumann and Marine (1931), in the course of their early observations on the effect of injecting anterior pituitary extract in rabbits, observed that glycosuria was temporary, and tended to decrease after the 14th day of injection. This disappearance of the glycosuria was believed by these workers to be due to a deterioration in the potency of the extract with keeping, but the possibility that the rabbits were becoming resistant to the action of the extract was also considered. No evidence was produced that the extract did in fact deteriorate with keeping and in the light of the experiences of other observers there can be little doubt that the latter explanation was the correct one, and that the disappearance of the glycosuria was the result of a change in the response of the animals to the extract rather than

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any alteration in the extract itself. E.I. Evans (1933) investigated the effect of injecting anterior pituitary extract in dogs and found that hyperglycaemia could be produced by this method, but it was noticed that the hyperglycaemia disappeared after a period of about one week and was replaced by subnormal blood sugar levels even if the injections were continued. Young (1936), Houssay (1937) and Long (1937) also commented on the fact that the hyperglycaemia produced by the injection of extract of the anterior lobe of the pituitary was of a temporary nature. Shpiner and Soskin (1934) confirmed the finding that the hyperglycaemia produced in dogs by injecting anterior pituitary extract disappeared when the extract was continued and that hypoglycaemic levels might be observed in spite of the continued administration. These workers however carried the matter further by proving that this compensatory response was the result of a reaction on the part of the pancreas. This proof was obtained by demonstrating that if the pancreas was removed from the animal the extract continued to produce a hyperglycaemia as long as it was administered.

Until very recent times there has been almost universal agreement that the hyperglycaemia following injection of anterior pituitary extract in animals was only temporary. Evans and his colleagues (1931) formerly were the sole dissentients from this view. These workers were able to produce glycosuria in 2 dogs by injecting extract of the anterior lobe of the pituitary, the glycosuria persisting for some weeks after the injections were stopped./

stopped. With this exception however the production of permanent glycosuria and hyperglycaemia had not been secured by the injection of anterior pituitary extract in experimental animals until Young published his results in 1937. Young managed to produce a permanent diabetic state in 2 out of 3 dogs by injecting them with extract obtained from 25 to 35 grams of anterior pituitary substance daily. This observation is of the greatest importance as an illustration that the resistance of the pancreas may be permanently overcome by injecting large quantities of anterior pituitary extract and will be considered in some detail later.

Badenoch and Morris in their study of the effect of anterior pituitary extract on children were unable to produce any diminution in sugar tolerance in 2 normal children by this means, any change resulting being in the nature of an increase in glucose tolerance.

The work of Richardson and Young (1937) represents an approach to this problem of the response to the injection of anterior pituitary extract from another direction. These workers studied the effect produced by the injection of extract of the anterior lobe of the pituitary on the size and number of the islets of Langerhans in the pancreas of the rat and discovered that the islets became larger in size and more numerous as the result of this treatment. The authors concluded from their results that the anterior pituitary extract used, although capable of producing hyperglycaemia and glycosuria in the dog, contained a substance

which/

which stimulated the hypertrophy of islet-tissue in normal rats. The possibility that the hypertrophy of the islets of Langerhans which was observed might be due to a compensatory response to the 'diabetogenic' properties of the extract, prompter and more effective in the rat than the dog was also considered but was rejected since the blood sugar levels of normal rats treated with the extract for a period of some days showed no significant alteration from the normal. The absence of any evidence of hypoglycaemia as the result of injection of the extract over a period of time provided no support for the hypothesis that the hypertrophy observed was due to a compensatory response, but the authors did not rule out this possibility entirely. The present writer inclines to the opinion that a compensatory response on the part of the pancreas provided a better explanation for the findings of Richardson and Young, and one more in keeping with that of other investigators, although it is freely admitted that it is at present impossible to reconcile this opinion with the observation that no alteration was noted in the level of the blood sugar. On the other hand if the islet hypertrophy is the result of the presence of an unknown substance in the extract then it is still extraordinary that the level of the blood sugar should remain unaltered unless the new-formed islets are incapable of producing insulin.

The results of the various investigators which have been quoted demonstrating the probability, to say the least of it, of a compensatory response to the 'diabetogenic' action of

anterior/

anterior pituitary extract in the case of the experimental animal affords considerable support to the opinion already expressed in this study that the results are explainable on this basis, so far as the anterior lobe of the pituitary is concerned.

A study of the literature makes it apparent that the effect of continued administration of the extract of the posterior lobe of the pituitary has not been investigated with the same frequency as that of the anterior lobe, almost all workers having concerned themselves with the immediate effect alone. The only record of any observations on the results produced by continued injection of posterior pituitary extract that the author has been able to discover in the literature occurred in the course of a report by Whitehead and Darley (1931) on a case of diabetes insipidus. The individual studied by these workers exhibited glycosuria in addition to the usual signs of diabetes insipidus and was given injections of extract of the posterior lobe as a therapeutic measure. After a period of this treatment the glycosuria disappeared and Whitehead and Darley suggested that this might be due to a raising of the renal threshold for glucose by the action of the extract. However the blood sugar curves that the authors give as being taken before and after treatment show that there was an appreciable lowering of the peak value of the curve obtained after treatment as compared with that secured before any extract was given. This finding, although not commented on in the original paper, resembles those obtained in the present investigation and is perfectly compatible with the conclusion that the disappearance/

disappearance of the glycosuria in the patient might be attributed to an improvement in glucose tolerance brought about by the injection of extract of the posterior lobe of the pituitary, without invoking any hypothetical increase in the renal threshold for glucose. That is to say the continued administration of posterior pituitary extract may bring about an increase in tolerance to glucose in the same way as has been shown for anterior pituitary extract in the present study.

From the evidence presented in this study and from that available in the literature it is concluded that there is a similarity in the action of extracts of the anterior and posterior lobes of the pituitary so far as their effect on carbohydrate tolerance is concerned, and that this similarity is probably the result of stimulation of the pancreas to secrete more insulin. If the most popular views on the mode of action of these two extracts are accepted the response is evoked in the case of the anterior lobe extract by its action in stimulating the process of gluconeogenesis, and in the case of the extract of the posterior lobe by its action in inhibiting the peripheral action of the insulin initially secreted. In both instances the eventual result is the secretion of a quantity of insulin more than sufficient to compensate for the contra-insular action of the extract.

This conclusion that the two extracts exhibit a similar effect on tolerance to glucose must be modified to a certain extent. It only holds good when the effect of the extract is studied in the manner adopted in this study: there is no intention/

intention at the present time to maintain that the action of the two extracts would be found to be the same if the problem were investigated in another manner. For example, there is no justification in concluding from the results obtained in this investigation that extract of the posterior lobe of the pituitary would be as powerful a 'diabetogenic' agent as that of the anterior lobe if its action were studied in the experimental animal, following pancreatectomy or otherwise. Indeed, all the evidence on this subject points to a conclusion that the posterior lobe extract is much weaker in this respect (Houssay and Biasotti, 1931b). Another reservation that must be made concerning the validity of the conclusion which has been reached concerns the daily quantities of the extracts used. These were chosen in a more or less arbitary manner and there is no guarantee that similar results would have been obtained if the daily quantity of posterior pituitary extract had been doubled or halved. That is to say the results obtained must depend to some extent on the fact that the quantities used should be comparable in the strength of their contra-insular action. This was evidently the case with the dosage used.

Another important point must be made clear: it is not intended to maintain that both lobes of the pituitary are of equal importance in the regulation of carbohydrate metabolism in the human subject. Earlier workers in this field were of the opinion that the posterior lobe was of principal importance in this/

this respect (Geiling and others, 1927) but, as has been outlined, it has been clearly established within recent years that it is the anterior lobe and not the posterior that plays the chief part, and indeed the place to be assigned to the posterior lobe is a matter of some doubt. Nevertheless this recognition of the secondary importance of the secretion of the posterior lobe of the pituitary in the regulation of the body carbohydrate does not invalidate the conclusion reached in the present study, that the extracts of both lobes produced a similar effect and by stimulating the same response. In whatever manner the secretion of the anterior lobe of the pituitary produces its contra-insular action the ultimate result is an increase in the total amount of circulating carbohydrate and it is this increase that has been judged to evoke the compensatory response. Therefore it can be argued that any method by which a similar increase in the circulating carbohydrate can be secured will be capable of securing a similar response, that is to say, an increase in the glucose tolerance. Extract of the posterior lobe of the pituitary has been shown to be capable of producing an increase in the glucose of the blood, possibly by inhibiting the action of insulin, and although its mode of action is not the same as that of extract of the anterior lobe it is easy to understand why the ultimate result is the same. Whether the secretion of the posterior lobe is produced in sufficient quantities in health to produce this effect, or, to put the question in another way, whether the posterior lobe of the pituitary is of any importance in carbohydrate metabolism

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is beside the point. The fact remains that extract of the posterior lobe of the pituitary when given by injection in healthy human subjects has been shown to be capable of causing an increase in the tolerance of the individual to carbohydrate, in the same way as has been shown to occur after the injection of anterior pituitary extract.

The results obtained can therefore be all explained by considering the contra-insular action of the extracts employed, and the increase in tolerance which has been observed to occur after the continuous administration of these extracts may be attributed to a compensatory response on the part of the individual, probably pancreatic in origin.

Section Six.

The Effect of Injection of Extract of the Adrenal Medulla on Carbohydrate Tolerance.

In the previous section it has been shown that the ultimate effect produced by the continued administration of posterior pituitary extract is similar to that secured when anterior pituitary extract is used, if the problem is studied in the manner described. The conclusion was reached that, in whatever manner the secretion of the anterior lobe of the pituitary produced its effect, the ultimate result was to provoke an increase in the quantity of glucose in the circulation and this was considered to be responsible for the compensatory response observed. It was argued that a similar response might be expected to occur if the same increase in the blood sugar was secured by means of injecting posterior pituitary extract, and experimental evidence was advanced to show that this was, in fact, the case. It was very convenient to regard the results which had been observed when extracts of both lobes of the pituitary were administered as being due simply to the consequent increase in the quantity of circulating glucose, but it was soon realized that this explanation simplified the problem overmuch. The hypothesis advanced in this way implied that the action of the anterior lobe of the pituitary in the experiments/

experiments described could be satisfactorily explained by a consideration of the resulting hyperglycaemia. This conclusion comes very near to saying that similar results could be obtained by giving glucose to the subject by mouth. The position becomes manifestly absurd in view of the experimental work of others showing the profound and complicated influence on carbohydrate metabolism exerted by the anterior lobe of the pituitary. Furthermore it has been repeatedly shown that the administration of glucose by mouth over a period of time always results in an increase of glucose tolerance and under ordinary conditions temporary failure, such as has been described as happening when anterior pituitary extract was given, does not occur. As will be shown later, under special conditions it is possible to produce a temporary failure of glucose tolerance by increasing the carbohydrate intake but not without special preparation of the subject to be examined. In view of these considerations it became necessary to re-examine the problem and seek for another, more satisfactory explanation of the findings recorded.

One aspect of the action of anterior pituitary extract which had been neglected was its power of neutralising to some extent the hypoglycaemic action of insulin. It has been shown (di Benedetto, 1933) that the prolonged administration of extract of the anterior lobe of the pituitary to dogs results in a state of resistance to the action of insulin being produced. In the case of extract of the posterior pituitary lobe a similar power of abolishing the hypoglycaemic action of insulin has been observed (Burn, 1923). It seemed likely, as regards the present investigation/

ation, that too little attention had been paid to this important property of the extracts used, and it became necessary to enquire whether the neutralization of insulin by the extracts was of importance in providing an explanation for the results observed. For this purpose it became necessary to extend the present investigation to determine whether it was possible to produce a temporary failure of glucose tolerance, such as had been shown to occur with the administration of extracts of the anterior and posterior lobes of the pituitary, by means of inducing a hyperglycaemia from endogenous sources without using any substance known to be capable of producing a condition of insulin resistance.

The Action of Extract of the Adrenal Medulla on Carbohydrate Metabolism. It has long been known that the injection of adrenalin in the intact experimental animal is followed by a rise in the blood sugar level, and it has been securely established that this hyperglycaemia can largely be attributed to the acceleration of the breakdown of glycogen in the liver. However it has recently become apparent that the sustained rise in the blood sugar produced in this way could not be accounted for simply by an outpouring of glucose from endogenous sources, unless there occurred at the same time a retarding of the utilization of the blood sugar by the peripheral tissues. The arguments in favour of the opinion have been advanced by Cori (1931) and can be conveniently summarized as follows: in order to produce a hyperglycaemia comparable to that following/

following the injection of adrenalin, it is necessary to infuse into the intact animals a quantity of glucose greater than the total amount of glucose stored as glycogen in the liver as well as that newly formed from protein sources during the experiment. Therefore either adrenalin stimulates the formation of glucose from fat, or after its injection the rate of utilisation of glucose is retarded at the same time as hepatic glycogen is broken down. As there is no evidence of the formation of glucose from fat the second suggestion was accepted by this worker as representing the course of events following the injection of adrenalin. Again, it has been shown that while the hyperglycaemia following the ingestion of glucose is characterized by an increase in the difference between the blood sugar levels of arterial and venous blood, the hyperglycaemia following the injection of adrenalin results in little or no increase in this difference. (Cori and Cori, 1929a; 1929b). These latter observations were interpreted as demonstrating the action of adrenalin in inhibiting the utilization of glucose by the peripheral tissues.

Although this conception of the inhibitory action of adrenalin was useful insofar as it provided an explanation for its action on carbohydrate metabolism it was obviously at variance with what was known of the action of adrenalin in general (Himsworth and Scott, 1938b). The general action of adrenalin had been previously summarized by Cannon (1915) in the "emergency theory" which postulates that its effect is to facilitate rapid and efficient

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action of the body. But if adrenalin inhibits the utilization by the muscles of carbohydrate, on which they normally rely for their energy, its action would certainly not facilitate a rapid and efficient action of the body, indeed its effect would be in the reverse direction. Himsworth and Scott (1938b) recorded experiments which were intended to remove this discrepancy, and to permit a conception of the action of adrenalin on the metabolism of carbohydrate which was more in accord with what was known of its role in the rest of the body. These workers studied the effect of adrenalin injected in rabbits in which the liver had been excluded from the circulation, by comparing the course of the blood sugar with that in rabbits similarly prepared but not given adrenalin. In both groups the blood sugar level fell from the time that the liver was excluded from the circulation, and at the same rate, until the animals of one group were given adrenalin. In these animals the blood sugar dropped suddenly, remained steady for a few minutes at the new level, then commenced to decline keeping at a lower level than the control animals which were not given adrenalin. These observations were regarded as evidence of the action of adrenalin in <u>increasing</u> the rate of utilization of glucose by the peripheral tissues, the temporary cessation of the fall in the blood sugar after the injection of adrenalin being explained on the grounds than an inflow of glucose had taken place, at a rate sufficient to mask temporarily the increased utilization of glucose, from some unknown source. As

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there is no known peripheral source of blood sugar this suggestion was advanced with considerable diffidence, but if it is accepted that such a source possibly exists, then there is no difficulty in accounting ofr the observation that the height of the hyperglycaemia following the injection of adrenalin makes it impossible of explanation solely on the grounds of an acceleration of hepatic glycogenolysis, an inflow of glucose from an unknown peripheral source explaining the apparent deficiency. It is not intended to follow this argument further, since it is sufficient for present purposes to understand that Himsworth and Scott have presented a considerable body of evidence in favour of the fact that adrenalin, far from inhibiting the peripheral utilisation of glucose, encourages the uptake of glucose by the tissues. Therefore by using adrenalin it would be possible to study the effect of a hyperglycaemia from endogenous sources on glucose tolerance without any danger of producing a state of resistance to the action of insulin at the same time, such as has been shown to occur when extracts of the anterior and posterior lobes of the pituitary are used.

Methods. The subjects were selected as in the previous experiments, and blood sugar curves were carried out before and after the administration of adrenalin, and also after a rest period. The action of adrenalin in increasing the rate and power

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of the heart action was an undesirable side effect and made it necessary to use small doses; for this purpose it was decided to give 0.3 c.cm. of adrenalin hydrochloride 1:1000 solution as the standard dose. In view of the fact that the mode of action of adrenalin on the blood sugar differed from that of anterior and posterior pituitary extracts, being in the one instance a short, sharp hyperglycaemia occurring immediately after the injection, and in the other a more gentle, remote effect, it was decided to give the adrenalin twice daily in order to prolong the length of time that the blood sugar was increased. In this way it was intended to make the conditions of experiment as equal as possible. Adrenalin hydrochloride 1:1000 was therefore injected in quantities of 0.3 c.cm. twice daily for varying periods of time.

Results. A total number of 32 subjects were given adrenalin hydrochloride in quantities varying from 1.8 c.cm. to 5.4 c.cm. and the effect on glucose tolerance noted. In 25 instances the effect seen was an increase in carbohydrate tolerance; in 5 cases the effect was negligible (a change in the peak value of less than 20 mg.); and in 2 instances a loss of tolerance was observed as a result. In neither of the cases in whom loss of glucose tolerance was observed to occur was the effect of continuing the administration of the extract tried, as was the case when anterior and posterior pituitary extracts were used. This omission was unavoidable and was due to the fact that there was no time available for further study in these cases. The information derived from the blood sugar curve carried out after the rest

period did not differ from that obtained when anterior and posterior pituitary extracts were used, that is to say there was a tendency for the blood sugar levels to reassume their former values, therefore in a number of instances the final curve was not carried out.

The results are summarized in Tables 7, 8 and 9, and in Fig. 7.

Discussion. The results which have been described following the administration of adrenalin over a period of some days show some differences from those which were obtained when extracts of the anterior and posterior lobes of the pituitary were used. When anterior pituitary extract was used in a total number of 34 cases a diminution in glucose tolerance was observed to occur in 8 instances (approximately 23 per cent.); in a series of 21 individuals treated with posterior pituitary extract a similar response was noted in 5 cases (approximately 24 per cent.); but when adrenalin was given in the same way to a group of 32 subjects a diminution in glucose tolerance was noted in only 2 instances (approximately 6 per cent.). As has been said previously the individuals in the 3 groups were chosen in the same way and although differences in age and sex exist the smallness of the numbers prevents any analysis being made taking into account these differences. With these exceptions which are unavoidable in the present investigation the three groups of subjects may be regarded as similar, and any difference in the results may be attributed

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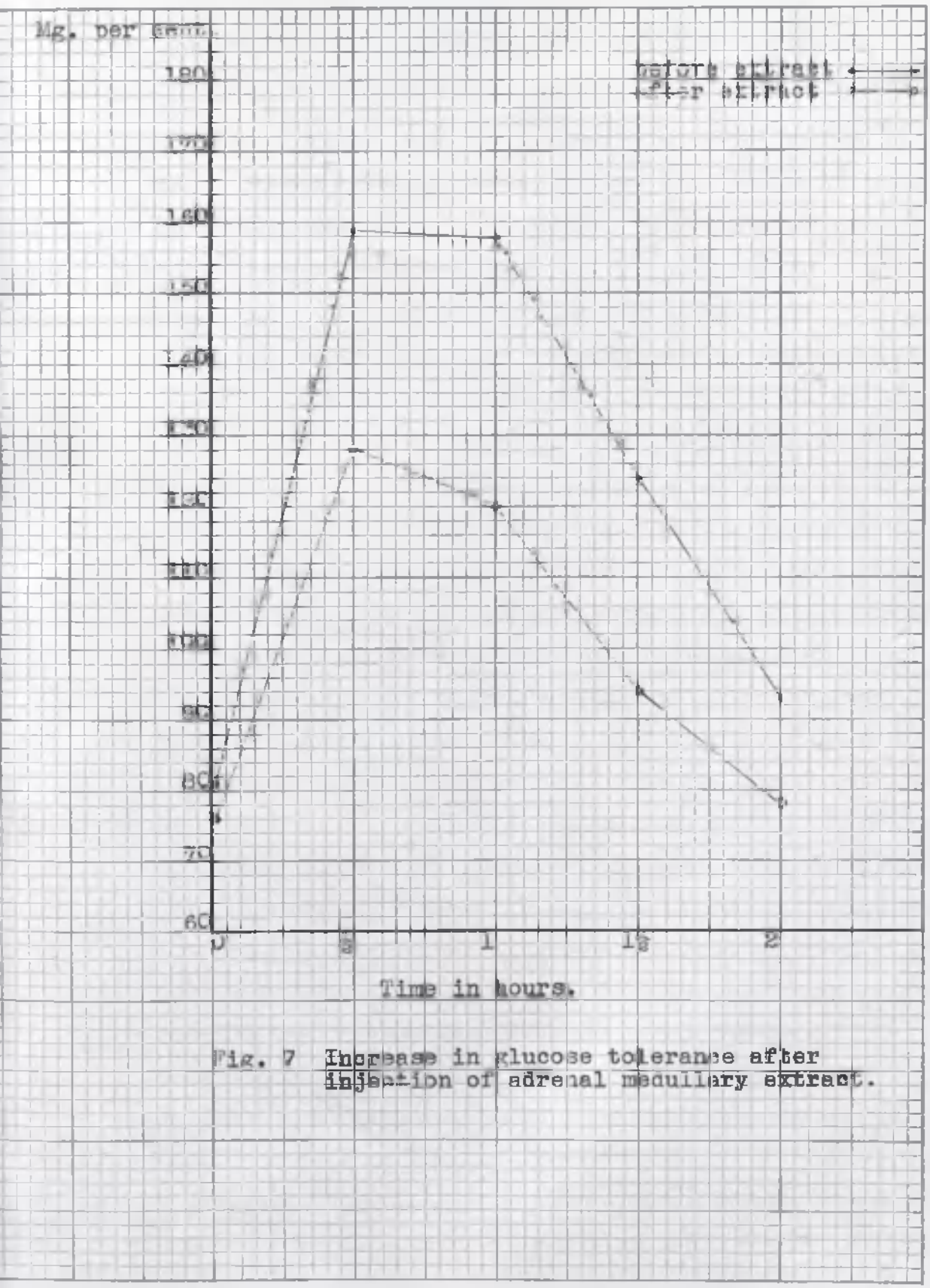

Fig. 7 Increase in glucose tolerance after injection of adrenal medullary extract.

the different properties of the extracts used. The important difference in the results is the comparative frequency with which some loss of glucose tolerance was secured by injecting anterior and posterior pituitary extracts, whereas when adrenalin was used loss of tolerance was rare. This loss of tolerance after giving adrenalin was observed in 2 cases only (Cases 81 and 82). In Case 81 there can be no doubt that the blood sugar curve obtained after adrenalin was given shows a diminution in glucose tolerance as compared with the first curve, but in Case 82 the only evidence that adrenalin produced a loss of glucose tolerance is that the blood sugar level at the ½ hour period is appreciably higher in the second curve than in the first. All the other values of the second curve are lower than the corresponding levels in the first curve. According to some observers the more rapid return to the fasting level shown in the curve taken after adrenalin was given might be taken as evidence that tolerance had <u>increased</u> as the result of treatment, but according to the criterion for comparing different blood sugar curves adopted in this investigation this cannot be accepted. Sufficient has been said to show that only in one instance was there unequivocal evidence of adrenalin producing a diminution of glucose tolerance. It would have been much more satisfactory if it had been possible to show that in no instance had adrenalin been capable of producing a loss of glucose tolerance but it is unreasonable to expect any biological experiment to inhibit such clear cut differences, in such experiments there are always a few cases which run a course contrary to the majority, but it is submitted that the results obtained after the use of adrenalin differ sufficiently from those obtained after the use of anterior and posterior pituitary extract

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to warrant further comment.

When the pituitary extracts were used it was apparent in a considerable proportion of the individuals examined that the effect of the extracts was to produce a temporary loss of glucose tolerance. This was regarded as being evidence of a temporary failure on the part of the pancreas to respond to the stimulus; the subsequent improvement in tolerance occurring when the administration of the extracts was continued being regarded as indicating that adequate compensation had taken place. It was shown that this apparent stimulation of pancreatic activity was not due to any specific property of the anterior pituitary alone since a similar result was obtained when extract of the posterior lobe was substituted, and therefore this action was present in extracts from both lobes. In view of the fact that both extracts were known to be capable of causing an increase in the quantity of glucose in the circulation it was suggested that the findings could be adequately explained on this basis, the conclusion being reached that the improvement in tolerance observed after the injection of pituitary extracts was accounted for by the stimulus of hyperglycaemia affecting the pancreas and resulting in an increased output of insulin. As was pointed out however, both extracts had another action in common, that of producing a state of resistance to the action of insulin, and since a hyperglycaemia from exogenous sources never caused a loss of tolerance under ordinary circumstances, it was necessary to examine the effect of an endogenous hyperglycaemia on the glucose tolerance without producing at the same/

same time any insulin resistance.

The injection of adrenalin hydrochloride twice daily in small quantities causes a hyperglycaemia from endogenous sources for short periods of time, but when this was carried out the effect was to cause an increase in glucose tolerance in the great majority of instances, a finding in contrast to that recorded when pituitary extracts were used. It is therefore submitted that although a hyperglycaemia from endogenous sources has been shown to be capable of producing a temporary loss of tolerance in a few instances the usual effect is to produce an increase in tolerance, and the rarity with which any loss of tolerance could be secured in this way makes it unlikely that the hypothesis hitherto advanced in explanation of the results obtained with pituitary extracts provides a satisfactory answer. It is impossible to arrive at a definite conclusion on this point in an investigation based on the present lines but it is most probable that a factor other than the production of a hyperglycaemia is responsible for the findings obtained when pituitary extracts were used. From a review of the properties of these extracts it seems that their ability to inhibit the action of insulin may play a decisive role in the production of a temporary loss of tolerance. By injecting extracts of the anterior and posterior lobes of the pituitary not only is the quantity of glucose in the circulation increased but the insulin secreted in response to this increase is neutralised for a time; under these circumstances it is not surprising that some temporary failure of tolerance results until adjustment/

adjustment has been made to the new conditions. It is accordingly concluded that although the possibility that the production of a hyperglycaemia by itself explains the results, the probability is that the production of a state of resistance to the action of insulin is also of great importance.

If this explanation is correct then there is no longer any need to maintain the absurd conclusion that the effect of the anterior lobe of the pituitary on glucose tolerance can be explained satisfactorily on the grounds that a rise in the blood sugar is produced, in other words that this action might be duplicated by increasing the intake of carbohydrate in the diet.

It has been demonstrated that anterior pituitary extract has the property of inducing some loss of glucose tolerance and that this property is shared with extract of the posterior lobe but it is again emphasized that this statement only holds good under the conditions of the present experiment; there is no intention to maintain that the anterior and posterior lobes of the pituitary are of equal importance in the regulation of carbohydrate metabolism under normal circumstances, or even that the posterior lobe is of any importance at all in this respect in normal physiology. The literature is indefinite on this point but, as will be recalled, the general opinion is that the anterior lobe is of paramount importance and that the posterior lobe may have a similar but weaker action so far as its 'diabetogenic' properties are concerned. Returning to the findings of the present experiment it is evident that, under the conditions laid down,

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the extract of the adrenal medulla is at the most much less effective than pituitary extracts in causing a loss of tolerance to glucose, and if the hypothesis that an endogenous hyperglycaemia by itself is largely incapable of reducing glucose tolerance is correct, then the adrenal medulla should be of minor importance in the production of diabetic states. A large amount of work has been done on experimental animals in this field but only a few recent and authoritative communications will be considered in order to illustrate that the conclusion adopted in the preceding sentence is not entirely untenable.

Reference has been made to the observation that removal of the hypophysis results in a remarkable amelioration of diabetes in the experimental animal. This finding is of fundamental importance and has been repeatedly confirmed, but in addition many workers have investigated the effect produced on pancreatic diabetes by removal of other endocrine glands. At present it is of interest to review the findings recorded when adrenalectomy is performed in the depancreatized animal. It is unfortunate that there exists a great confliction of opinion on the effect of adrenalectomy; Leloir (1935) found that removal of the adrenals did not modify pancreatic diabetes in the dog with the exception of some diminution in severity which might occur at a late stage of the experiment; this may be regarded as confirmation of the earlier work of Lewis and Turcatti (1924) who observed that adrenalectomy did not modify the diabetes in depancreatized animals if the state of nutrition was good, but some amelioration might occur in the last stages. These last workers also made the important observation/

observation that removal of the pancreas after adrenalectomy produced a diabetes just as intense as in normal animals. On the other hand Houssay and Biasotti (1936) found that removal of the adrenals modified pancreatic diabetes in the toad while Long and others (1937) made a similar observation observation in the case of dogs and cats.

This direct confliction of opinion makes it very confusing for the impartial observer but fortunately it is unnecessary for the purpose of the present investigation to take sides in the argument. If adrenalectomy does not modify pancreatic diabetes then extract of the adrenal gland must possess negligible diabetogenic activity as compared with the secretion of the pituitary, a finding in keeping with the observations made in connection with the present investigation. On the other hand if it is concluded that adrenalectomy is capable of causing an amelioration of pancreatic diabetes then further comment is necessary. Long with his several co-workers has been responsible for the majority of recent detailed studies on the influence of the adrenal on carbohydrate metabolism and a review of the work of his school has been published (Long, 1937). In this it is stated that depancreatized cats in which the adrenal medulla has been denervated, or in which the adrenal medulla has been removed, succumb rapidly to the diabetes following pancreatectomy; in these animals the excretion of glucose, nitrogen and ketone bodies is almost identical with that in cats subjected to pancreatectomy alone.

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In rats if the medulla is completely removed the remaining cortical cells regenerate and the cortex is restored in a period of from 10-18 days. If this operation of medullectomy is carried out in depancreatized rats the glycosuria disappears and then rises to its previous level; if removal of the cortex is now performed glycosuria disappears and does not return. Therefore Long concludes that the removal of the adrenal medulla does not ameliorate pancreatic diabetes and points out that if surgery in man has been successful in relieving diabetes by denervation of the medulla it is only due to the consequent cortical damage.

The conclusion that is drawn from this short review of the literature is that all the evidence points to the fact that the secretion of the adrenal medulla has no 'diabetogenic' activity, and so adrenalin differs in this respect very strongly from extract of the anterior lobe of the pituitary, and to a lesser degree from extract of the posterior lobe of the pituitary which probably has a slight action in this respect. It is contended that the results of the present investigation are quite in keeping with those of other workers, with the exception that on the present results alone it would appear that posterior pituitary extract is almost equal in activity with anterior pituitary extract. This apparent error may well be explained on some unrecognised discrepancy in the comparative doses of the extracts used as has been previously pointed out; it is not intended to study this particular question further since the experiment was designed to investigate the action of extract of the anterior pituitary in human/

human subjects and not the comparative activity of extracts of the anterior and posterior lobes.

Throughout this communication reference has been frequently made to the apparently contradictory results obtained by groups of workers carrying out what are presumably identical experiments. Repetition of the experiments with careful control of the results will probably eliminate much of this contradiction, but what appears to have aggravated the confusion is the construction of weighty hypotheses based on a few observations in a restricted field. For example, the removal of the hypophysis in experimental animals has been shown repeatedly to result in an increased sensitivity to the hypoglycaemic action of insulin (Houssay and Magenta, 1927; Hartman and others, 1930; di Benedetto, 1933; Corkill and others, 1933; Daggs and Eaton, 1933; Barnes and others, 1934; Marks, 1936), but hypophysectomy is not the only way in which increased insulin sensitivity can be produced since the removal of other endocrine glands has a similar effect. It has been shown to follow removal of the thyroid (Houssay and Busso, 1924; Ducheneau, 1924; Burn and Marks, 1925; Britton and Myers, 1928), and after adrenalectomy (Lewis and Magenta, 1925; Britton and others, 1928; Scott and others, 1934; Zucker and Berg, 1937). The position is further complicated by the findings of Chaikoff, Reichert, Larson and Mathes (1935) who observed that in dogs the operation of craniotomy and retraction of the right temporal lobe of the brain was sufficient to increase the sensitivity of the animals/

animals to insulin, and by the observation of Ingram and Barris (1936) that damage to the hypothalamic area in cats might lead to a similar condition. The fact that increased sensitivity to insulin does develop after these various operative procedures seems well established but the interpretation of the findings offers a confused picture. The influence of hypophysectomy itself is regarded as sufficient explanation for the majority, but others would have it that it is the secondary atrophy occurring in one or other of the endocrine glands subsequent to loss of the hypophyseal hormones that is responsible. For example Corkill and his co-workers (1933) suggested that atrophy of the thyroid might account for the insulin sensitivity, but for Long (1937) it is the loss of adrenal cortical activity that provides the explanation. This particular result, increased sensitivity to the hypoglycaemic action of insulin, has been observed as following numerous widely different procedures and there is naturally a great temptation to seek for a factor common to all in explanation, but it is not essential, nor even probable, that there is a single common factor concerned in its production. The same end-result may be produced in a variety of ways, and this has been clearly demonstrated in the present investigation in which it has been shown that the injection of 3 different substances having different actions may produce the same final state. The secretion of the anterior lobe of the pituitary is most generally regarded as stimulating the process of gluconeogenesis, that of the posterior lobe inhibits the peripheral action of insulin, and adrenalin/

adrenalin accelerates the breakdown of hepatic glycogen, but the injection of each of these extracts may result in an increase in glucose tolerance.

Many other examples could be given of more or less unsuccessful attempts to provide a single explanation for a phenomenon known to occur after various different procedures have been carried out, but it is considered that sufficient has been said to indicate that the same apparent end-result may be produced by different mechanisms and it is only when a study is made on a wide basis that the truth of this assertion becomes apparent. Neglect of this principle will probably lead to the formulation of faulty hypotheses which if not carefully examined will tend to conceal the truth.

Table 7.

Increase in Glucose Tolerance after Injection of Adrenal Medullary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c cm.
56.	45 yr.	F.	Peptic ulcer.	0	98	196	202	179	129	
				4.8 c.cm.	92	137	114	90	81	-65
				6 days.	87	127	133	145	106	
57.	29 yr.	F.	Peptic ulcer.	0	93	143	212	166	121	
				4.8 c.cm.	81	159	151	86	80	-53
				5 days.	87	128	130	123	91	
58.	48 yr.	M.	Mitral Disease.	0	71	172	210	182	121	
				4.8 c.cm.	82	149	117	104	80	-61
				6 days.	74	145	156	134	99	
59.	55 yr.	F.	Anxiety Neurosis.	0	74	182	198	169	126	
				3.6 c.cm.	73	117	147	97	80	-51
				4 days.	81	188	162	155	123	
60.	39 yr.	M.	Peptic ulcer.	0	72	182	170	111	59	
				2.4 c.cm.	78	159	127	88	60	-23
				4 days.	74	164	150	119	73	
61.	67 yr.	M.	Peptic ulcer.	0	74	151	184	110	66	
				4.2 c.cm.	71	134	140	103	58	-44
				6 days.	78	164	134	97	79	
62.	33 yr.	M.	Disseminated sclerosis.	0	82	144	182	93	61	
				3.6 c.cm.	66	135	112	74	62	-47
				5 days.	70	133	142	70	65	

Table 7. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg/100 c. cm.
63.	34 yr.	M.	Acute Rheumatism.	0	75	128	116	108	84	
				3.6 c.cm.	63	104	95	72	61	-24
				5 days.	72	125	112	62	80	
64.	25 yr.	M.	Acute Rheumatism.	0	75	158	135	85	90	
				3.6 c.cm.	66	122	100	74	66	-36
				5 days.	62	131	123	72	68	
65.	31 yr.	M.	Acute Rheumatism.	0	70	149	166	105	75	
				3.0 c.cm.	72	92	78	66	60	-74
				5 days.	71	117	102	57	78	
66.	20 yr.	M.	Normal.	0	101	212	164	126	90	
				3.0 c.cm.	91	124	176	101	78	-36
				4 days.	83	172	125	105	81	
67.	65 yr.	M.	Obesity.	0	111	175	156	126	90	
				3.6 c.cm.	70	139	95	90	96	-36
				5 days.	86	182	151	123	105	
68.	25 yr.	F.	Goitre.	0	94	158	171	160	114	
				2.4 c.cm.	82	146	139	76	80	-25
				5 days.	97	145	164	125	88	
69.	31 yr.	F.	Anxiety Neurosis.	0	97	190	178	160	116	
				3.6 c.cm.	86	128	145	133	117	-45
				6 days.	97	156	185	132	101	

Table 7. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg/100 c. cm.
70.	38 yr.	F.	Pleurisy.	0	81	156	182	163	131	
				3.0 c.cm.	72	114	136	130	125	-46
				5 days.	90	172	149	133	105	
71.	16 yr.	F.	Rheumatoid Arthritis.	0	85	96	116	129	113	
				6.6 c.cm.	75	86	103	104	95	-25
				7 days.	84	100	107	103	105	
72.	64 yr.	F.	Peptic ulcer.	0	85	186	166	133	115	
				4.8 c.cm.	73	154	166	109	88	-20
				5 days.	76	179	169	122	95	
73.	38 yr.	M.	Peptic ulcer.	0	70	200	143	110	62	
				4.2 c.cm.	80	161	133	94	79	-39
				7 days.	74	141	130	66	57	
74.	18 yr.	F.	Acute Rheumatism.	0	72	114	166	111	92	
				3.6 c.cm.	78	139	125	106	61	-27
				6 days.	84	142	106	75	61	
75.	21 yr.	F.	Pleurisy.	0	80	157	111	93	77	
				5.4 c.cm.	72	129	133	102	77	-24
				8 days.	71	106	125	120	105	
76.	39 yr.	M.	Bronchitis.	0	74	122	127	132	100	
				1.8 c.cm.	71	101	78	79	73	-26
77.	21 yr.	M.	Spondylitis.	0	70	141	128	106	78	
				1.8 c.cm.	65	108	84	88	85	-33

Table 7. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg/100 c. cm.
78.	27 yr.	F.	Rheumatoid Arthritis.	0	74	156	98	68	56	
				1.8 c.cm.	76	121	76	102	50	-35
79.	31 yr.	M.	Peptic ulcer.	0	76	149	154	115	94	
				1.8 c.cm.	82	130	126	94	72	-24
80.	23 yr.	F.	Neuritis.	0	71	169	115	95	75	
				1.8 c.cm.	66	112	102	76	84	-57
Mean:					81	159	158	124	93	
					75	128	120	94	78	
					80	146	138	106	88	

Table 8.

Decrease in Glucose Tolerance after Injection of Adrenal Medullary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mg/100 c.cm.
81.	71 yr.	F.	Venous Thrombosis.	0	79	134	151	145	123	
				4.8 c.cm.	79	151	189	179	156	+38
				5 days.	79	145	175	189	139	
82.	38 yr.	M.	Peptic ulcer.	0	74	159	127	106	73	
				2.4 c.cm.	72	192	112	93	62	+33
				5 days.	76	145	157	132	80	
Mean:					77	147	139	126	98	
					76	172	150	136	109	
					78	145	166	160	110	

Table 9.

No Significant Alteration in Glucose Tolerance after Injection of Adrenal Medullary Extract.

Case.	Age.	Sex.	Disease.	Total Amount of Extract. / Duration of Rest Period.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall mg./100 c.cm.
83.	32 yr.	M.	Peptic ulcer.	0	74	100	143	130	83	
				1.8 c.cm.	74	159	115	73	69	+16
84.	47 yr.	F.	Nephritis.	0	76	137	128	93	57	
				1.8 c.cm.	74	136	117	90	60	-1
85.	28 yr.	F.	Erythema Nodosum.	0	75	122	109	93	97	
				1.8 c.cm.	69	122	134	94	90	+12
86.	52 yr.	F.	Auricular Fibrillation.	0	68	139	114	88	82	
				2.4 c.cm.	70	119	125	100	94	-14
87.	32 yr.	F.	Pleurisy.	0	71	112	163	118	87	
				3.6 c.cm.	83	145	122	104	60	-18
				6 days.	81	132	111	80	67	
Mean:					72	102	131	104	81	
					74	136	103	92	75	

Section Seven.

The Relationship between the Daily Intake of Carbohydrate and the Degree of Glucose Tolerance.

It has previously been noted that a difference was apparent in the blood sugar curves obtained from those individuals who gained in tolerance as the result of administration of anterior pituitary extract, as compared with the curves secured from those who lost tolerance. Of the group of 17 subjects who gained tolerance after injection of the extract 16 had peak values of more than 150 mg. On the other hand in the group who lost tolerance this distinction was not so evident, only 3 of the 8 cases having peak values over 150 mg. Moreover in 3 instances in which loss of tolerance occurred 'flat' blood sugar curves were obtained suggesting a resemblance to the children with coeliac disease studied by Badenoch and Morris. It was considered that these results were sufficiently striking to warrant further investigation in the hope that some of the factors determining the nature of the response to the extract might be discovered. When the results obtained with posterior pituitary extract are studied the interest is not diminished since the same characteristics of the 2 groups can be observed. Adding the results, it is found that the administration of pituitary extracts caused an increase in glucose tolerance in 25 cases and of these 24 had peak values of more than 150 mg./

150 mg., whereas in 13 instances where a loss of tolerance was observed only 5 cases had a peak value of more than 150 mg. These findings were regarded as suggestive that a relationship might exist between the peak value of the initial blood sugar curve and the type of response to pituitary extracts.

Of all the factors that influence the height of the blood sugar curve, and therefore the degree of glucose tolerance, the most carefully studied has been the quantity of carbohydrate in the diet. Accordingly it seemed reasonable to investigate whether there was any relationship between the total amount of dietary carbohydrate and the response to pituitary extracts. As a preliminary a short review was made of the influence of the carbohydrate intake on glucose tolerance.

Among the first to investigate the effect of a large intake of carbohydrate on the blood sugar level were Haman and Hirschman (1919) who made the important observation that if the same dose of glucose was given to human subjects at intervals of 90 minutes the glucose tolerance improved with each successive dose. The explanation of this finding advanced by these workers was that the repeated ingestion of glucose stimulated the mechanism responsible for the removal of glucose from the blood, the state of knowledge concerning the regulation of the blood sugar not permitting any more exact definition. In 1922 however Foster was able to advance a more definite explanation when he attributed the greater tolerance seen after a second dose of glucose to the effect/

effect of the insulin secreted in response to the first dose. The same results were demonstrated in another fashion by Thalheimer and his co-workers (1926) who showed that a continuous intravenous injection of glucose at a uniform rate resulted in a rise in the blood sugar which was followed by a decline to normal or even subnormal levels, and suggested that this response might be the result of a stimulation of the islets of Langerhans to produce more insulin, the stimulus being provided by the circulating glucose.

Interest in this problem has not been entirely directed towards the study of the way in which the individual responds to glucose given as such, either by the mouth or by intravenous injection, as exemplified in the experiments which have been described: the influence of the quantity of dietary carbohydrate has also been studied with great thoroughness. Sweeney (1927) investigated the effect of starvation on sugar tolerance, and also the influence exerted by the administration of protein, carbohydrate and fat. He regarded the beneficial effect produced on glucose tolerance by a high carbohydrate diet as being the result of the sensitization of the insulin producing mechanism by the stimulus of excessive carbohydrate consumption. Conversely, the adverse effect on carbohydrate tolerance produced by starvation and a diet containing large quantities of fat was attributed to the absence of this stimulus. Macleod (1930) was in complete agreement with this explanation, and expressed the opinion that when there was an abundance/

abundance of pre-formed carbohydrate entering the circulation the islets of Langerhans were stimulated to produce larger quantities of insulin than usual, and to secrete it more abundantly in response to temporary increases in the blood sugar.

The conclusion reached by these workers, that an increase in the intake of carbohydrate produces an increase in the amount of insulin secreted by the pancreas, secures additional support from the results obtained in the course of researches on the factors controlling the secretion of insulin in the experimental animal. For example, Kosaka (1933) observed that the infusion of a solution of glucose into the pancreatico-duodenal artery of the decapitated cat produced a rapid fall in the blood sugar level, much more rapid a fall than occurred when a similar injection was made into the femoral artery or portal vein in similar animals. From this evidence it is concluded that the secretion of insulin is in the main governed by the glucose level of the blood arriving at the pancreas. The work of the Houssay school on this subject of the control of insulin secretion has been most comprehensive and has been summarized by Houssay in a recent publication (Houssay 1937). It has been demonstrated that the presence of a pancreatic graft in the neck of a dog is capable of preventing the rise in blood sugar which follows pancreatectomy in an animal without such a graft; similarly if the graft is inserted into a dog already suffering from pancreatic diabetes the blood sugar falls to normal levels within 2 or 3 hours and then remains within normal limits, if the graft is then removed hyperglycaemia reappears. Since the pancreatic graft in these experiments has no nervous connections and yet, since

it/

it is apparently capable of controlling the blood sugar level, secretes insulin the only possible stimulus for insulin secretion in these circumstances is the glucose level of the circulating blood. Further evidence that this is the case is afforded by injecting glucose intravenously into a dog whose sole pancreatic tissue is represented by the presence of a pancreatic graft in the neck. When this is done the resulting blood sugar curve resembles that obtained in the intact animal closely, there being only slight differences which are accounted for by the absence of any nervous control of the pancreatic tissue. Again, if one, two or even three pancreases are grafted into a dog the blood sugar level remains within normal limits, the secretion of insulin being evidently decreased and adjusted so that the total output of insulin is sufficient to maintain a normal blood sugar level. As the result of the findings recorded it is concluded by Houssay that although the pancreas maintains the normal blood sugar level by secreting insulin, in its turn the blood sugar level regulates the secretion of the pancreas, stimulating it by hyperglycaemia and inhibiting it by hypoglycaemia. Therefore the blood sugar level regulates the secretion of insulin.

The foregoing may be regarded as an expression of the most generally held opinion concerning the control of insulin secretion, but all workers are not in agreement and several other opinions have been expressed on this point. However it is not intended to devote space to a consideration of the several hypotheses advanced concerning this subject but it is necessary to consider one/

one of them at this time, since an understanding of it is essential to appreciate arguments that will be brought forward in a later section. Himsworth (1933) while recognising the importance of the finding that glucose tolerance improved when the carbohydrate of the diet was increased was not wholly satisfied that an increase in the secretion of insulin provided a completely satisfactory explanation. He pointed out that it had long been recognised that the efficiency of similar doses of insulin might vary from time to time when given to cases of diabetes mellitus: the presence of infection usually called for a considerable increase in insulin dosage; in diabetic coma hundreds of units might be necessary in order to produce any appreciable alteration in the blood sugar level, but after the individual emerged from coma small doses might result in a state of hypoglycaemia; more insulin was required to control the rise in the blood sugar following a quantity of carbohydrate eaten in the morning, than would be necessary to produce a similar effect after the same quantity taken later in the day: and that in some cases a condition of insulin resistance might arise in which huge doses of insulin made no alteration in the level of the blood sugar. Another point of importance was the observation that an increase of the carbohydrate allowance in the diet of a diabetic did not necessarily mean an increase in the dose of insulin. Under these circumstances it appeared that the efficiency of insulin had been increased and investigations were conducted on this apparent potentiation of insulin. It was observed (Himsworth, 1933)/

1933) that when the individual was taking a high carbohydrate diet the injection of a standard dose of insulin was followed by a shorter latent period and a more rapid fall in the blood sugar than when the individual was taking a high fat diet. The conclusion was drawn that insulin as prepared and as secreted was an inactive substance and required activation possibly by the action of a kinase which might be produced by the liver. In a further study (Himsworth, 1934) it was established that similar results could be obtained with experimental animals, and that the improvement in tolerance which resulted from a high carbohydrate diet could be explained better on the basis of increased efficiency of secreted insulin than on an increase in the amount of insulin secreted by the pancreas. Later, experiments were conducted (Himsworth, 1935) to show that the improvement in tolerance on a high carbohydrate diet was determined neither by the caloric value of the diet, nor by any change in the ketogenic-antiketogenic ratio, nor change in the fat nor protein content of the diet, but solely by the amount of carbohydrate present in the diet.

This work excited a great deal of attention and provoked much thought involving as it did new conceptions concerning the importance of the liver in the metabolism of carbohydrate and in diabetes mellitus. However, before the existence of an insulin kinase in the liver had been definitely disproved or otherwise by other workers Himsworth himself rejected the hypothesis in favour of another (Himsworth and Scott, 1938a). So far as the present investigation is concerned it is this later hypothesis that/

that is of interest and detailed reference will be made to it later, for present purposes it is not of primary importance whether hyperglycaemia results in an increased secretion of insulin, or whether the insulin secreted is made more active. What is important is that an increase in the intake of carbohydrate increases glucose tolerance and this may be regarded as an expression of raised pancreatic efficiency, in other words when the dietary carbohydrate is plentiful the blood sugar curve tends to be low, and since there is an apparent connection between the height of the blood sugar curve and the response of the individual to pituitary extracts the influence of the composition of the diet on that response must eb investigated.

Section Eight.

The Influence of the Carbohydrate Content of the Diet on the Response to Pituitary Extracts.

In order to study this problem the following procedure was adopted:

Method. The subjects chosen for the investigation were selected from in-patients as in the previous experiments. To begin with these individuals were given a diet containing a total daily ration of carbohydrate amounting to 50 grams and precautions were taken that this allowance was not exceeded. This low carbohydrate diet was continued for a period of one week in order to allow the subject to become accustomed to the unusual conditions, and at the end of this time a glucose tolerance test was carried out. Thereafter extract of the anterior lobe of the pituitary was injected in quantities of one c.cm. daily for 3 days and the glucose tolerance again estimated on the fourth day. On the completion of the test the subject was given a high carbohydrate diet containing a daily ration of 500 grams of carbohydrate and again a period of one week was allowed for stabilization followed by a glucose tolerance test. Anterior pituitary extract was then given in the same amount and for the same length of time as before and the effect estimated by a final blood sugar curve. Some of

the patients experienced difficulty in consuming the total allowance of carbohydrate and when this was encountered the deficiency was made up by providing drinks containing the required amount of glucose. In this way it was ensured that the total daily allowance of carbohydrate was taken in some form or another.

Assessment of Results. In a previous section mention has been made of the considerable difficulty in comparing blood sugar curves carried out on the one individual at different times, and in order to minimise any possible source of error in drawing conclusions based on negligible alterations in the blood sugar curves, it was decided that no change would be regarded as significant unless there was a difference of more than 20 mg. in the peak values of the curves. This arbitary choice of a standard is regarded as having been fully justified since it ensured that the conclusions would not be based on negligible changes in glucose tolerance, but it was realized that it was not invariably accurate as a means of assessing glucose tolerance. It was considered that since the activity of the extracts in altering glucose tolerance had been established it was justifiable to classify the responses according to the peak values of the blood sugar curves without requiring an alteration of at least 20 mg. In actual practice it turned out that those cases which did not exhibit an alteration in the peak value of the curves of more than 20 mg. a consideration of the other values of the curves compared left no reasonable doubt that they had been classified correctly. The results were accordingly classified according as to whether a

rise/

rise or fall had been recorded in the peak values of the curves as the result of the injection of anterior pituitary extract.

Results. The reactions of 10 individuals were studied in the manner described. When the results were examined it was found that when anterior pituitary extract was given, while the patient was taking a diet poor in carbohydrate, the effect was to increase glucose tolerance in 8 out of the 10 cases. When the high carbohydrate diet was provided the results obtained with the extract were very different, 9 of the 10 individuals exhibiting a loss of glucose tolerance. These results are summarized in Table 10 and Figs. 8 and 9.

These findings lend considerable support to the view that there is some connection between the quantity of carbohydrate in the diet and the nature of the response to extract of the anterior lobe of the pituitary; the nature of this relationship will be discussed in some detail later. For the present it was necessary to determine whether there was evidence of a similar relationship in the case of posterior pituitary extract, as seemed likely.

Method. The method adopted to study the effect of the carbohydrate intake on the response to posterior pituitary extract was identical with that which has been described for extract of the anterior lobe, except that the subjects were given posterior pituitary extract in doses of 0.5 c.cm. daily for the three day period. The results were assessed in the same way as were those obtained with anterior pituitary extract, that is to say any rise

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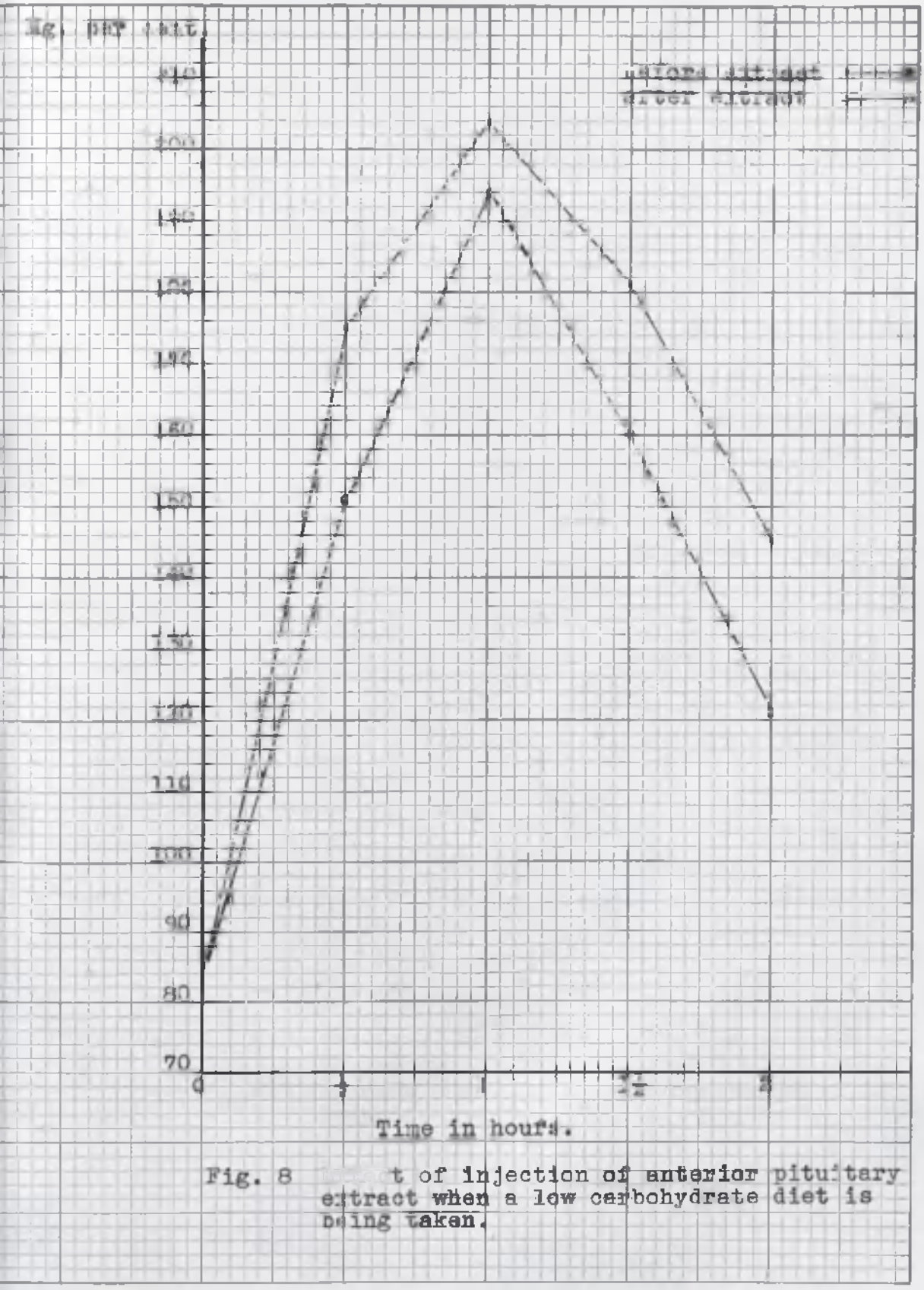


Fig. 8 Effect of injection of anterior pituitary extract when a low carbohydrate diet is being taken.

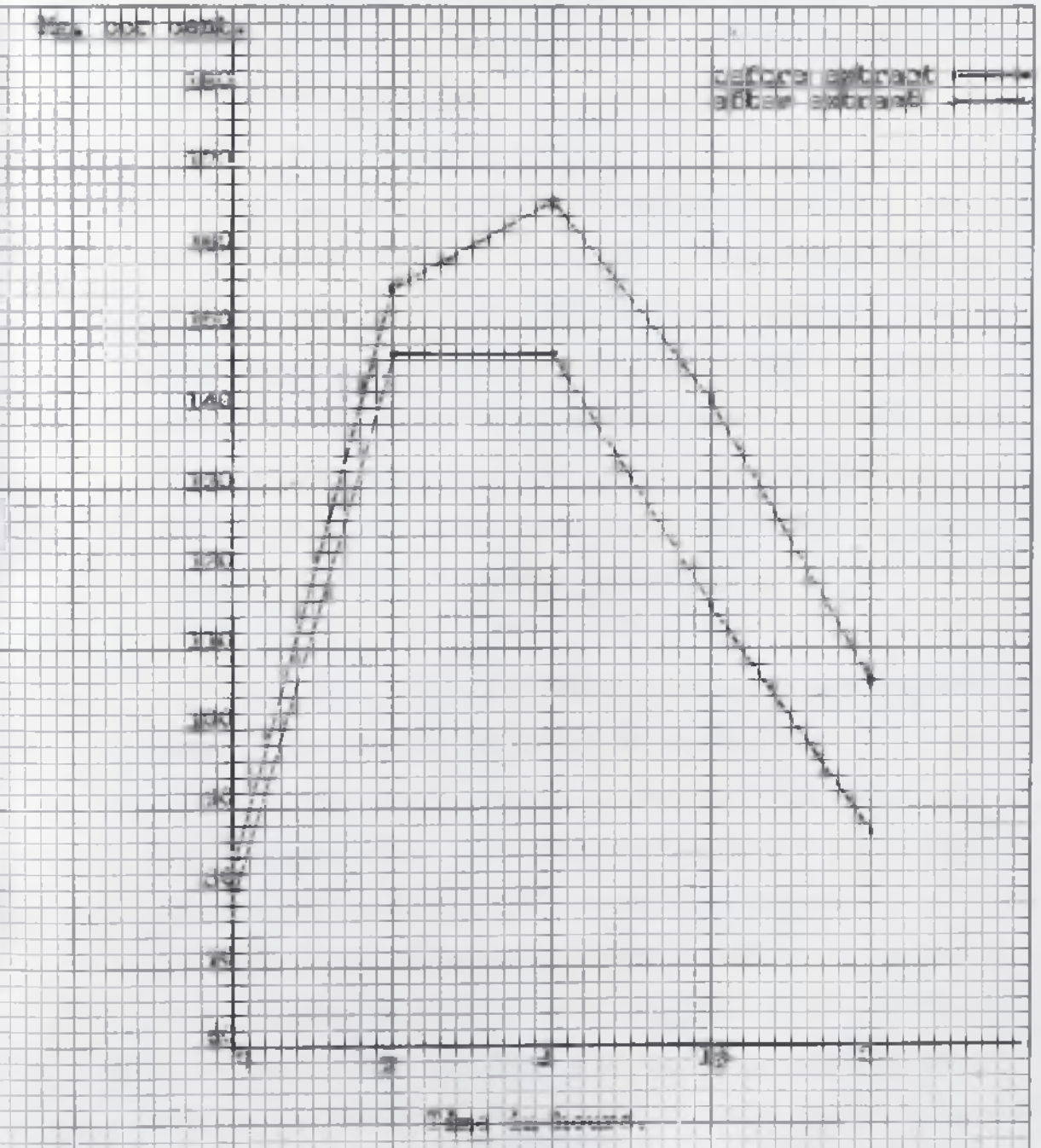
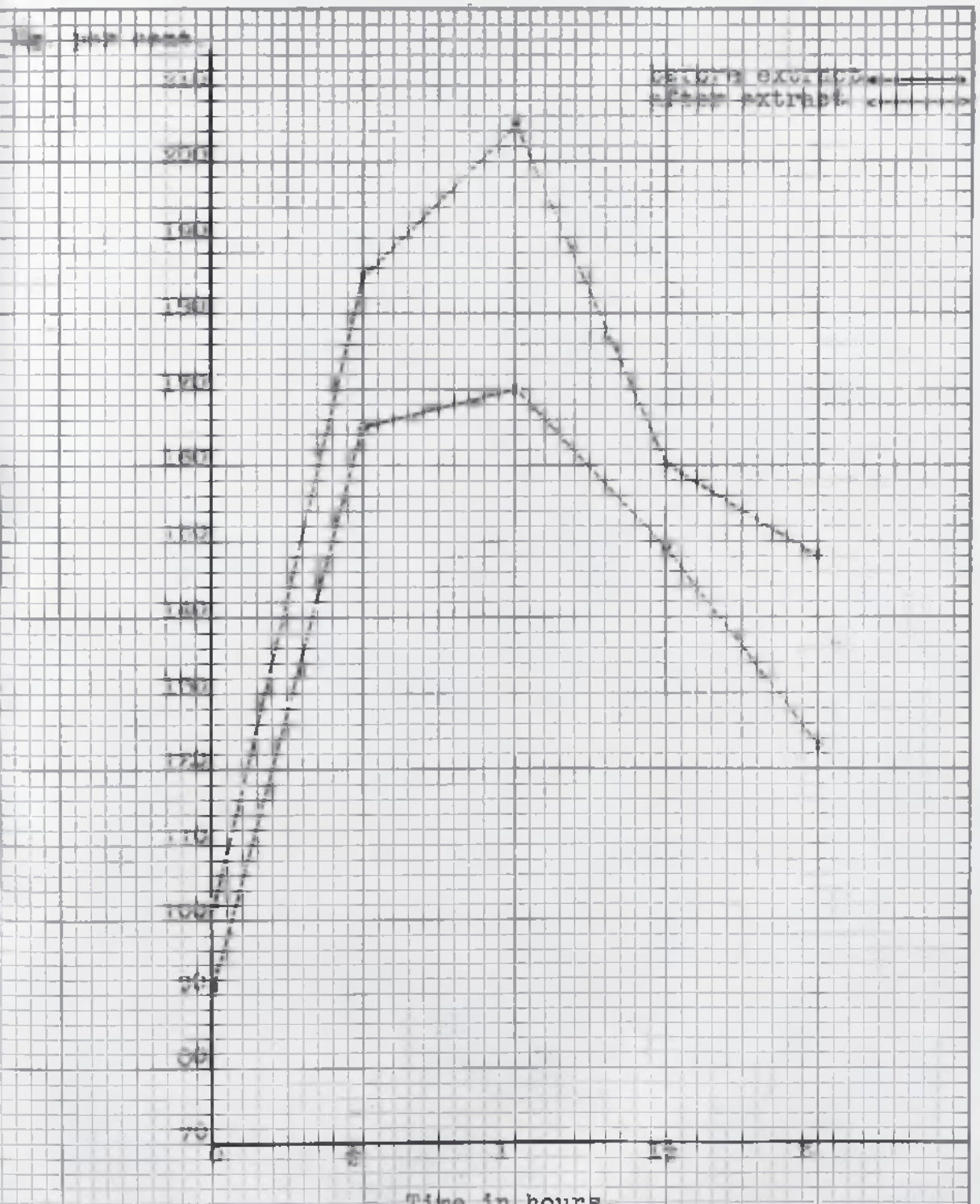


Fig. 9 Effect of injection of anterior pituitary extract when a high carbohydrate diet is being taken.

in the peak value was regarded as indicating that tolerance had lessened, and vice versa.

Results. Seven subjects were studied in the manner described and the results obtained were similar to those secured when anterior pituitary extract was used. When the low carbohydrate diet was being taken the effect produced by injecting posterior pituitary extract was an increase in glucose tolerance in 6 out of 7 cases; when the high carbohydrate diet was substituted the results were reversed, 6 of the 7 cases losing tolerance. These results are summarized in Table 11 and Figs. 10 and 11.

Discussion. These findings are considered as additional evidence that anterior and posterior pituitary extracts are similar in their action when studied in the way adopted in the present investigation. When the results obtained in both groups are considered it can hardly be denied that the daily intake of carbohydrate is a factor of importance in determining the nature of the response to pituitary extracts. Of the total of 17 individuals on whom the effect of altering the carbohydrate value of the diet was tried 14 showed increased glucose tolerance when the pituitary extracts were administered while a diet low in carbohydrate value was being consumed; on changing to a high carbohydrate the response to the pituitary extracts was altered, 15 of the 17 cases showing a diminution in tolerance. By changing the carbohydrate content of the diet it was therefore possible to alter the nature of the response to the extract in the/



Time in hours.

Fig. 10 Effect of injection of posterior pituitary extract when a low carbohydrate diet is being taken.

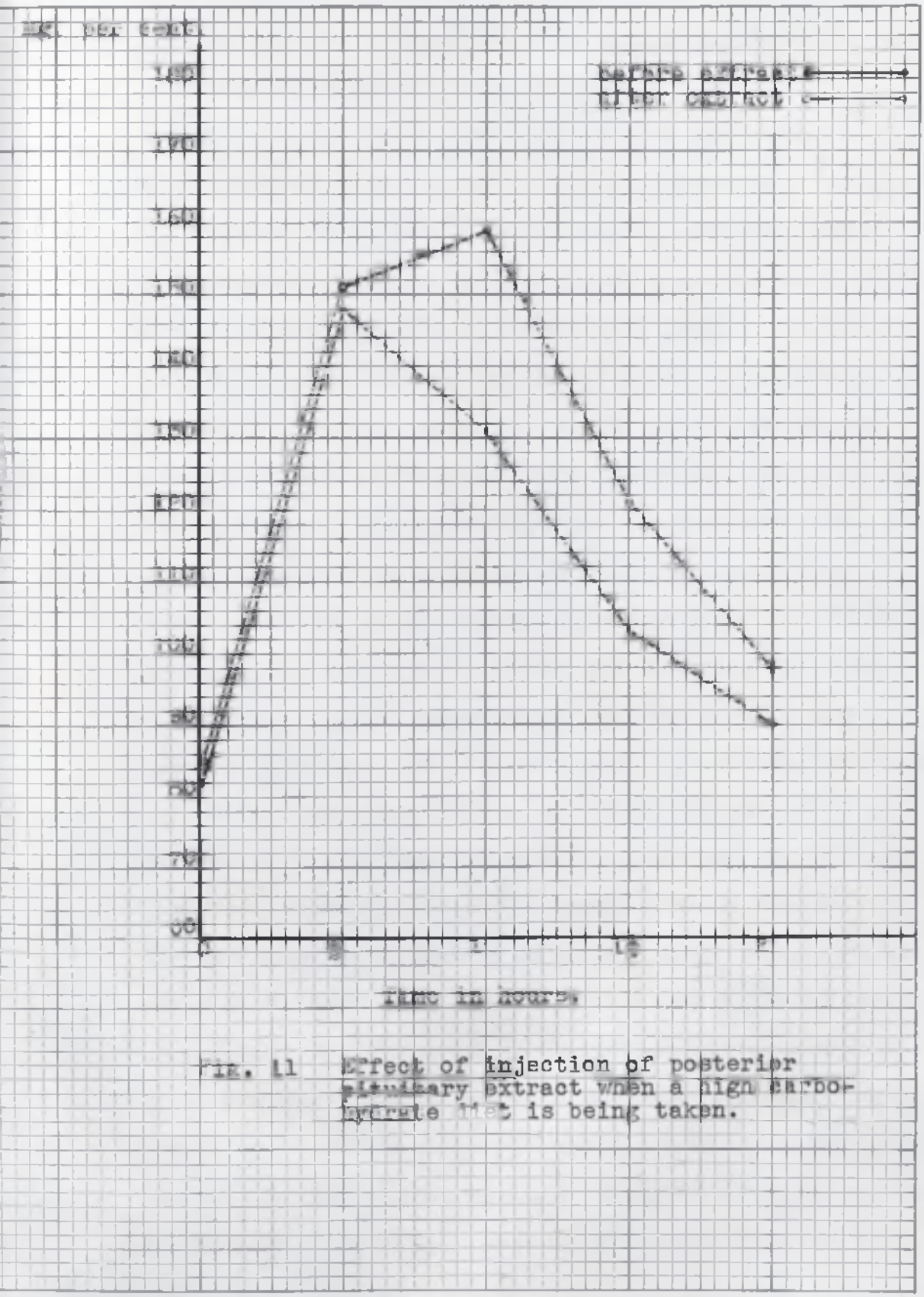


Fig. 11 Effect of injection of posterior pituitary extract when a high carbohydrate diet is being taken.

the great majority of instances. It is necessary to search for an explanation of these findings.

It has already been pointed out that the daily amount of carbohydrate taken in the diet is of great importance in deciding the tolerance of the individual to glucose. When the dietary carbohydrate is plentiful the glucose tolerance is high, probably as the result of an increased production of insulin; conversely, a reduction in the carbohydrate content of the diet results in a diminution of glucose tolerance. Now it has already been concluded that the alterations in glucose tolerance which follow the administration of extract of either the anterior or the posterior lobes of the pituitary is partly the result of a compensatory action on the part of the pancreas to the increased quantity of glucose in the circulation. It has also been shown that this is not the only factor operative but that most probably some degree of insulin resistance plays a part. Nevertheless whatever the relative importance of these factors in determining the response to injected pituitary extract, it has been clearly shown that the contra-insular action is capable of being overcome so that eventually an increase in tolerance results. Therefore the action of the extracts is to put a certain load on the individual, most probably on the pancreas. A normal subject responds to a diet containing a daily allowance of 500 grams of carbohydrate by showing an increase in glucose tolerance, but it is reasonable to suppose that this response entails a certain effort on the part of the pancreas. Accordingly, when an additional load in the form

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of pituitary extract is provided the occurrence of a degree of failure is not difficult to understand, especially when it is remembered that some of the patients found the allowance of 500 grams of carbohydrate daily too much to be consumed with comfort, and the deficiency had to be made up by supplying glucose drinks. It can be accepted that in some cases this allowance was in excess of that ordinarily consumed, but in others the inability to take the full ration may have been due to the fact that the carbohydrate offered was mainly in 'dilute' form, such as cereals, bread, milk, fruit and vegetables, and this difficulty might not have been encountered if a part of the allowance had been given as sweets and other sources of concentrated carbohydrate.

When the individual was taking the diet containing only 50 grams of glucose as a daily ration the state of affairs is different from that which has just been described. It has been explained that the less carbohydrate the subject is given the worse his tolerance becomes, most probably because there is little in the way of a stimulus to the secretion of insulin. This diminution of glucose tolerance is a temporary state and readily disappears when the allowance of dietary carbohydrate is increased. This being so, and if it is admitted that part of the action of pituitary extract is to increase the quantity of circulating carbohydrate then it is not unreasonable to conclude that the action of pituitary extract in increasing glucose tolerance, when the individual is taking a diet poor in carbohydrate, is due to this increase in the blood sugar. In other words the injection of a

hyperglycaemic/

hyperglycaemic extract is capable of taking the place of the post-prandial hyperglycaemia which normally occurs when the individual is taking a diet containing a normal amount of carbohydrate, in so far as the stimulation of insulin secretion is concerned. Pituitary extracts therefore may be regarded as acting, under the conditions described, in a manner similar to that produced by increasing the allowance of dietary carbohydrate.

The conclusions drawn appear satisfactory so far as they go, but it cannot be claimed that they provide an explanation for all the changes observed. It can fairly be claimed that the connection between the amount of carbohydrate in the diet and the nature of the response to pituitary extracts has been demonstrated to be fairly close, but it has not been shown to be absolute. If it were so then there would have been no exceptions; all of the subjects on the high carbohydrate diet would have lost tolerance to glucose when given pituitary extracts, and all would have gained when taking a diet poor in carbohydrate, but this was not so. It is true that those who gave responses contrary to the usual run were in the considerable minority, but the fact that they did so is sufficient to indicate that the carbohydrate content of the diet is not the only factor operative in determining the nature of the response to extracts of the pituitary. Other factors must be sought.

Table 10.

The Influence of the Carbohydrate Content of the Diet on the Response to Anterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Amount.	Carbohydrate Allowance.	Blood Sugar mg/100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg/100 c.cm
88.	48 yr.	M.	Pernicious Anaemia.	0	50 gm.	83	132	178	166	122	
				3 c.cm.	50 gm.	92	153	224	230	171	+52
				0	500 gm.	88	168	194	172	102	
				3 c.cm.	500 gm.	83	139	192	212	142	+18
89.	72 yr.	M.	Pernicious Anaemia.	0	50 gm.	95	164	149	139	119	
				3 c.cm.	50 gm.	87	113	159	90	60	-5
				0	500 gm.	81	154	120	108	97	
				3 c.cm.	500 gm.	84	125	133	135	117	-19
90.	17 yr.	F.	Acute Rheumatism.	0	50 gm.	84	189	196	222	143	
				3 c.cm.	50 gm.	76	130	145	159	151	-63
				0	500 gm.	88	178	135	130	117	
				3 c.cm.	500 gm.	87	175	188	200	139	+22
91.	15 yr.	F.	Acute Rheumatism.	0	50 gm.	79	132	159	160	137	
				3 c.cm.	50 gm.	64	159	134	128	97	-1
				0	500 gm.	69	120	180	80	69	
				3 c.cm.	500 gm.	80	185	149	147	76	+5

Table 10. (Contd.)

Case.	Age.	Sex.	Disease.	Amount.	Carbohydrate Allowance.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg/100 c.cm.
92.	42 yr.	M.	Peptic ulcer.	0	50 gm.	85	164	169	108	78	
				3 c.cm.	50 gm.	88	169	197	125	64	+28
				0	500 gm.	78	147	115	78	60	
				3 c.cm.	500 gm.	89	185	137	91	78	+38
93.	34 yr.	F.	Peptic ulcer.	0	50 gm.	73	157	245	222	214	
				3 c.cm.	50 gm.	89	127	215	156	137	-30
				0	500 gm.	76	156	165	132	63	
				3 c.cm.	500 gm.	88	182	147	95	78	+17
94.	42 yr.	M.	Acute Rheumatism.	0	50 gm.	90	175	196	166	128	
				3 c.cm.	50 gm.	84	148	190	172	110	-6
				0	500 gm.	88	113	149	133	119	
				3 c.cm.	500 gm.	86	149	182	116	110	+33
95.	40 yr.	M.	Peptic ulcer.	0	50 gm.	83	184	189	138	108	
				3 c.cm.	50 gm.	85	162	141	106	83	-27
				0	500 gm.	76	141	122	98	65	
				3 c.cm.	500 gm.	84	142	193	120	94	+52
96.	32 yr.	F.	Rheumatoid Arthritis.	0	50 gm.	112	250	294	286	222	
				3 c.cm.	50 gm.	105	176	286	263	208	-8

Table 10. (Contd.)

Case.	Age.	Sex.	Disease.	Amount.	Carbohydrate Allowance.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg/100 c.cm.
96.				0	500 gm.	80	143	156	122	90	
				3 c.cm.	500 gm.	84	140	184	166	117	+28
97.	40 yr.	F.	Visceroptosis.	0	50 gm.	72	200	263	208	175	
				3 c.cm.	50 gm.	84	172	250	175	125	-13
				0	500 gm.	76	146	134	102	86	
				3 c.cm.	500 gm.	78	130	158	128	110	+12
Mean:					50 gm.	85	175	204	181	145	
						85	151	194	160	121	
					500 gm.	80	147	147	115	87	
						84	155	166	141	106	

Table 11.

The Influence of the Carbohydrate Content of the Diet on the Response to Posterior Pituitary Extract.

Case.	Age.	Sex.	Disease.	Amount.	Carbohydrate Allowance.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg/100 c. cm.
98	67 yr.	F.	Renal Calculus.	0	50 gm.	125	256	278	244	286	
				1.5 c.cm.	50 gm.	110	258	233	220	202	-20
				0	500 gm.	99	141	136	122	95	
				1.5 c.cm.	500 gm.	86	193	175	124	115	+52
99.	39 yr.	F.	Anaemia.	0	50 gm.	95	130	169	143	122	
				1.5 c.cm.	50 gm.	95	135	149	143	110	-20
				0	500 gm.	80	126	124	104	123	
				1.5 c.cm.	500 gm.	83	131	149	115	98	+23
100.	22 yr.	F.	Acute Rheumatism.	0	50 gm.	122	238	222	141	161	
				1.5 c.cm.	50 gm.	98	185	185	137	109	-53
				0	500 gm.	93	189	149	132	103	
				1.5 c.cm.	500 gm.	95	130	175	119	116	-14
101.	52 yr.	F.	Pernicious Anaemia.	0	50 gm.	122	175	250	169	163	
				1.5 c.cm.	50 gm.	94	122	156	169	139	-81
				0	500 gm.	82	163	130	105	93	
				1.5 gm.	500 gm.	82	181	175	137	90	+12

Table 11. (Contd.)

Case.	Age.	Sex.	Disease.	Amount.	Carbohydrate Allowance.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall mg./100 c.cm
102.	38 yr.	M.	Peptic ulcer.	0	50 gm.	82	172	141	98	89	
				1.5 c.cm.	50 gm.	83	151	114	81	79	-21
				0	500 gm.	79	114	105	85	64	
				1.5 c.cm.	500 gm.	86	139	112	92	74	+25
103.	54 yr.	M.	Peptic ulcer.	0	50 gm.	84	159	198	159	98	
				1.5 c.cm.	50 gm.	79	172	208	174	123	+10
				0	500 gm.	72	156	137	79	70	
				1.5 c.cm.	500 gm.	81	147	164	134	87	+8
104.	46 yr.	F.	Rheumatoid Arthritis.	0	50 gm.	82	165	178	163	118	
				1.5 c.cm.	50 gm.	78	135	145	120	101	-33
				0	500 gm.	72	148	139	94	82	
				1.5 c.cm.	500 gm.	81	139	166	127	106	+18
Mean:					50 gm.	102	185	205	160	148	
						91	165	170	149	123	
					500 gm.	82	148	131	103	90	
						85	151	159	121	98	

Section Nine.

The Effect of a Sudden Increase in the Dietary Carbohydrate on Glucose Tolerance, and the Effect of the Continued Administration of Pituitary Extracts while the Subject was taking a High Carbohydrate Diet.

When the method which was adopted for the investigation of the relationship between the carbohydrate intake and the response to pituitary extracts is examined, a certain defect is apparent. Two different diets were given each individual and these were of a different character from the ordinary ward diet. A period of one week was allowed so that stability might be reached before any extract was administered; this is not a generous time allowance and there is a very definite possibility that the subject had not completely adjusted himself to the unusual diet before the test extract was injected. As will be seen later there is indeed evidence that a state of stability was not reached in the case of a few of the subjects. The question that requires to be answered is whether the results obtained were due wholly or in part to the fact that a complete adjustment to the unusual quantity of carbohydrate provided had not been attained before any extract was given.

The possibility that the individual had not completely adjusted himself to the unusual diet before he was given the particular extract is most probably of little importance in the case of the low/

low carbohydrate diet. Even if it is agreed that the diminution of glucose tolerance as the result of the small ration of carbohydrate allowed was not yet complete by the time the extract was given, that is to say the glucose tolerance had not become as poor as it would have, had the individuals been taking the diet for a longer period of time, the results obtained when pituitary extract was given lose none of their significance. The important finding is that by administering extracts of the pituitary it was possible to produce an improvement in tolerance in the majority of cases such as would have occurred if the ration of carbohydrate had been increased. In the case of the high carbohydrate diet however the position is different. The subject had been taking a total daily quantity of 50 grams of carbohydrate for a total period of 10 days (one week before any extract was given and 3 days on extract) and then was suddenly changed to a diet containing an allowance of carbohydrate 10 times as great as that to which he was accustoming himself. The magnitude of this variation in the allowance of carbohydrate is very considerable, and is much greater than any that could be conceived as occurring in the ordinary course of life. To cope with an alteration in the diet of this magnitude would require considerable flexibility in the mechanism controlling the secretion of insulin, and it would not be surprising if temporary failure to cope with the sudden increase in the carbohydrate intake occurred in certain cases. Such indeed was observed.

A total number of 17 subjects were subjected to this sudden increase in the dietary carbohydrate and of these as many as 4 showed some evidence of failure to deal with the larger quantity,

as/

as judged by a glucose tolerance test carried out one week after the change had been made. Considerable emphasis has been placed on the fact that the response to pituitary extract could be altered by increasing the carbohydrate ration in the diet, and that when a liberal supply was provided a temporary failure of sugar tolerance occurred when the extract was injected. This finding was contrasted with that observed when a low carbohydrate diet was given and the conclusion was drawn that the total quantity of dietary carbohydrate was a factor of great importance in determining the production of lessened tolerance to glucose by the injection of pituitary extract. The main support of this conclusion was afforded by the effect of the high carbohydrate diet in altering the response of the individual to the extracts, but, as has been said, approximately one quarter of the patients subjected to the investigation showed that the increase in the ration of carbohydrate by itself was sufficient to produce a diminution in tolerance to glucose without the administration of any extract. These 4 cases are of especial interest and require consideration.

The inability to deal with the sudden increase in the carbohydrate intake occurring when the change was made from the low to the high carbohydrate diet is illustrated in Table 12 and Fig. 12. The first blood sugar curve shown in the Table for each case is the last one obtained when the subject was taking the low carbohydrate diet, that is to say the one obtained after the pituitary extract was given; the second curve is that obtained after the individual had been taking the high carbohydrate diet for the standard period of one week; the third curve is that obtained

after/

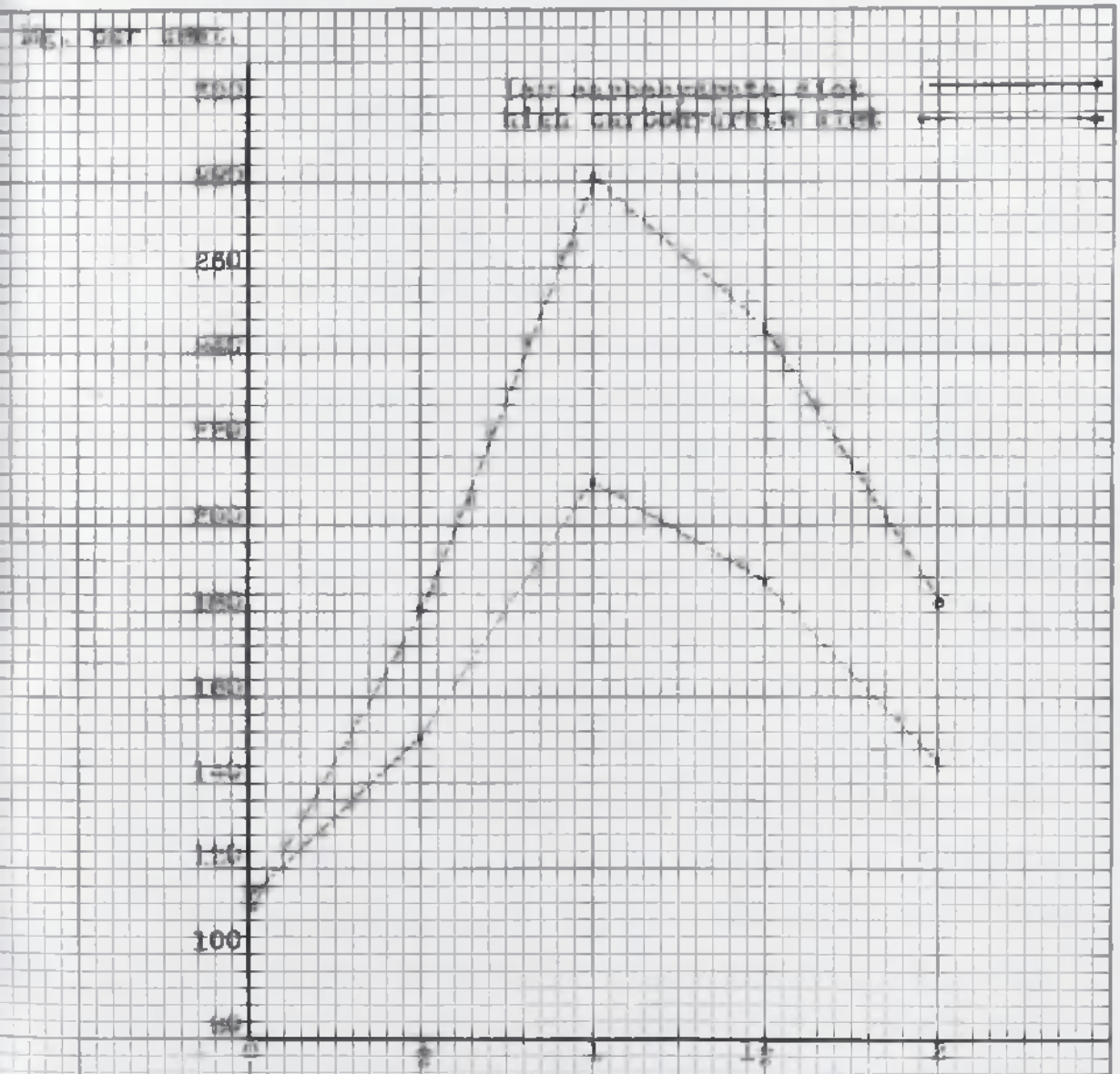

Fig. 12 — Temporary failure of carbohydrate tolerance on changing from a low to a high carbohydrate diet.

after the high carbohydrate diet had been taken for a further period of from 7 to 10 days as stated in the Table, and is the same as that given for the particular case in Tables 10 and 11 under the heading of '500 gm. carbohydrate diet'. It will be obvious that these 4 subjects required a considerable period of time to adjust themselves to the sudden great increase in carbohydrate intake, but that the loss of tolerance was of a temporary nature and recovery was ultimately made.

This observation is of considerable interest in showing that it is possible to produce a temporary loss of glucose tolerance by suddenly increasing the carbohydrate intake, but it cannot be claimed that it is of primary importance or that it opens new fields for study. Ever since the work of Sweeney (1927) all have agreed that a period of carbohydrate starvation lessens glucose tolerance, the present finding merely outlines another aspect of the picture, of some interest in demonstrating that a sudden, great increase in the dietary carbohydrate is in certain people capable of producing a temporary failure to cope with glucose, but actually breaking no fresh ground. What is of the greatest importance in the present investigation is that this finding casts some doubt on the validity of the conclusions drawn concerning the effect produced by an increase in the carbohydrate of the diet in deciding the response of the individual to the injection of extracts of the pituitary gland. In other words it must be determined whether it was the increase in the carbohydrate allowance that altered the effect of the extract, or whether the altered action of the extract that was observed was due wholly or in

part/

part to the fact that a period of one week was insufficient to allow the individual to become adjusted to the great increase in the carbohydrate intake. It was evident that the experiment had been badly planned in this respect and it became necessary to alter the conditions in order to answer the question.

There is also another matter which requires careful consideration. Hitherto it has been emphasized that any diminution in glucose tolerance produced by the injection of pituitary extracts has been temporary in nature and tends to disappear if the extract is continued, it is obviously of importance to decide whether the combination of the high carbohydrate diet and the pituitary extract might be capable of producing more than a temporary hyperglycaemia. During the course of the experiments just described the pituitary extracts were given for a period of 3 days and in the majority of instances a diminution in tolerance occurred when the subject was taking the high carbohydrate diet; it was decided that the period of administration of extract should be extended in order to ascertain whether a diabetic state could be produced by this means.

Method. A series of 16 subjects were selected as in the previous experiments; of these 7 were treated with anterior pituitary extract and 9 with posterior. The diet used was the same as that previously described and contained a daily allowance of 500 gm. of carbohydrate, but there was no preliminary period of carbohydrate starvation, as occurred before when the

low/

low carbohydrate diet was being taken, therefore since the subjects were taking ordinary diet before starting on the high carbohydrate diet the actual increase in the carbohydrate intake was not so great as in the previous experiments. In order to minimise still further any possibility of incomplete adjustment to the high carbohydrate diet on the part of the subject a period of 10 days was allowed before any injections were given.

Blood sugar curves were carried out before any extract was given. In the case of the extract of the anterior lobe of the pituitary one c.cm. was given daily for 3 days and the glucose tolerance again estimated, then the extract was continued in the same quantities for another period of 3 days and the blood sugar curve again examined. When posterior pituitary extract was used the quantity given was 0.5 c.cm. daily but otherwise the procedure was identical.

Results. When anterior pituitary extract was given to the 7 subjects taking a high carbohydrate diet a loss of glucose tolerance was noted as the result in 6 cases; the one exception was Case 107 in which a slight gain in tolerance was observed. These results were in keeping with previous findings but when the extract was continued in an attempt to increase the hyperglycaemia the diminution in tolerance was proved to be temporary and was seen to disappear in all but one instance (Case 110). In this subject the effect of continuing the injections for a still further period was observed with consequent disappearance of the hyperglycaemia/

glycaemia.

In the case of the 9 individuals who were subjected to similar treatment but who were given posterior pituitary extract the results were very similar. In every instance the effect of the extract was to cause a diminution in glucose tolerance but as with anterior pituitary extract this loss of tolerance was only temporary; when the extract was continued the loss of tolerance disappeared in 7 of the 9 cases. In the 2 cases (114 and 118) who showed a further loss of tolerance when the injections were continued, the effect of a further period of injections was not tried, but from the comparatively slight alteration in the curve that was produced by the second course of extract, there is no reason to believe that a progressive increase in the hyperglycaemia could have been secured. These results are summarized in Tables 13 and 14 and Figs. 13 and 14.

Discussion. The experiment which has just been described was conducted with the object of determining whether the conclusions arrived at in the previous part of the investigation could be justified, and also to decide whether a diabetic state might be produced by giving pituitary extracts while the subjects were taking a large daily allowance of carbohydrate. The results obtained confirm the finding that the hyperglycaemic properties of extracts of both lobes of the pituitary are enhanced when a liberal amount of carbohydrate is being consumed. There is however no evidence that diabetic state can be produced in this way by prolonging the period of administration of the extract, indeed/

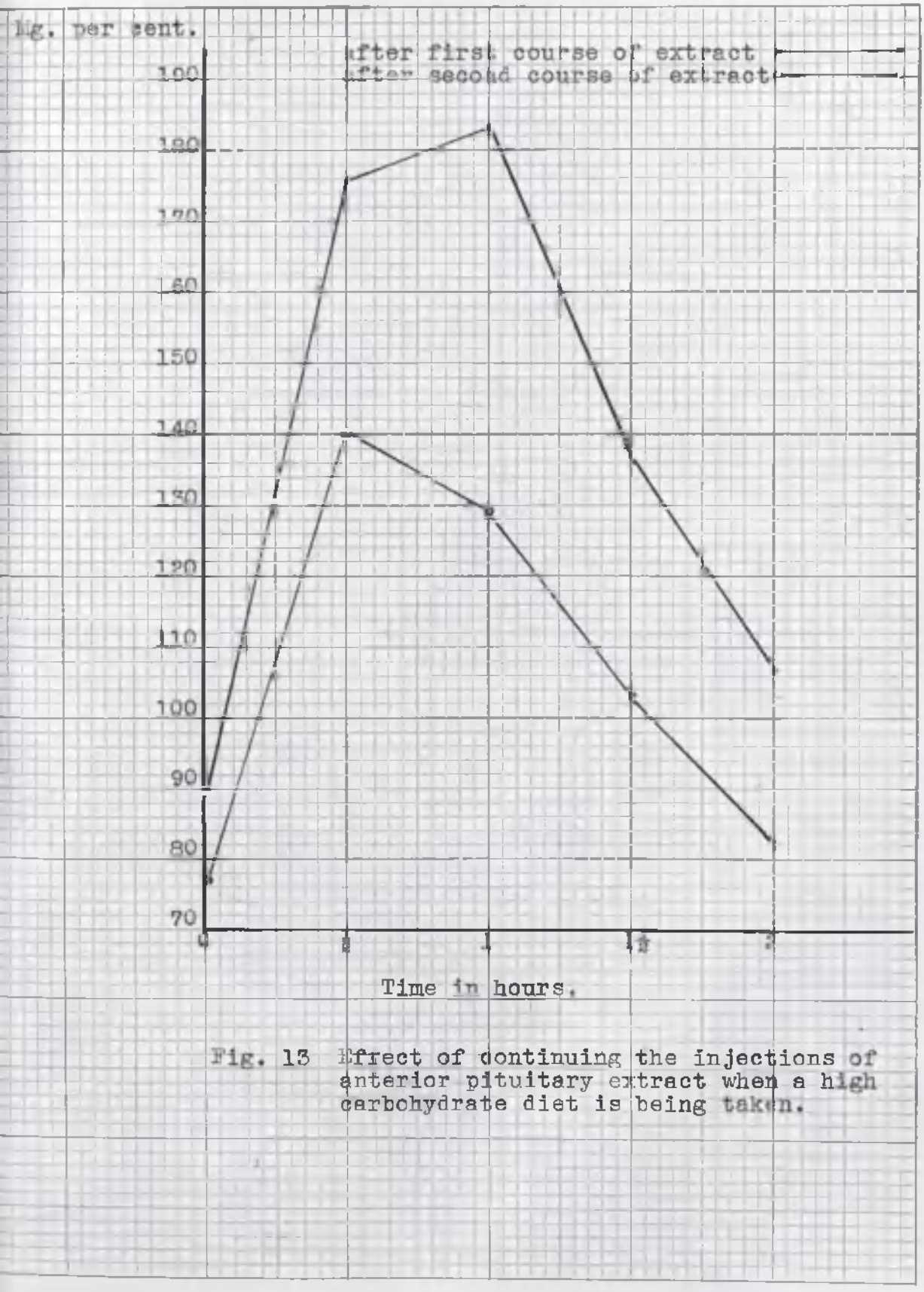

Fig. 13 Effect of continuing the injections of anterior pituitary extract when a high carbohydrate diet is being taken.

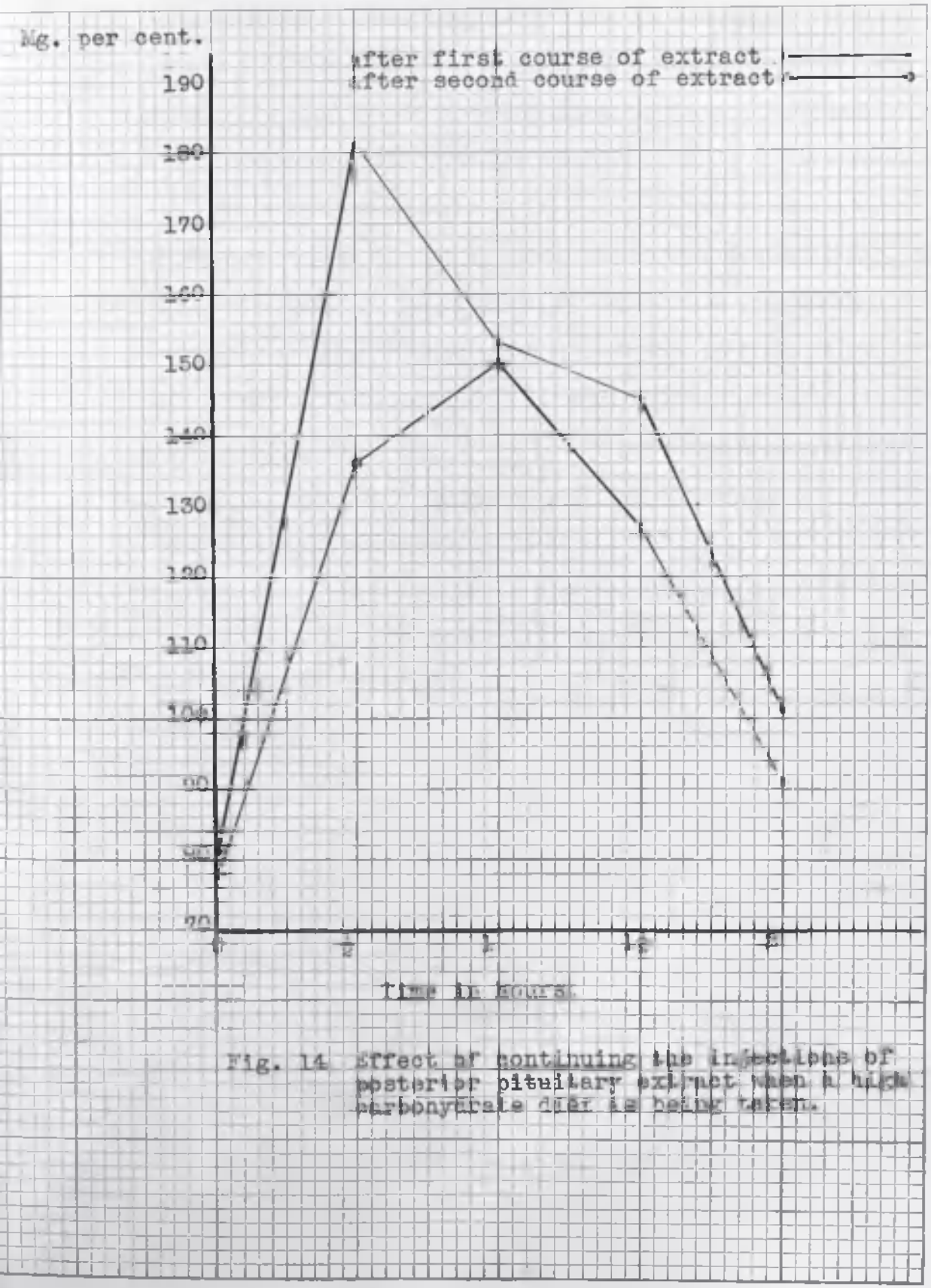

Fig. 14. Effect of continuing the injections of posterior pituitary extract when a high carbonydrate diet is being taken.

indeed all the evidence goes to confirm the observation previously made that any diminution in tolerance caused by injecting the extracts is only temporary and compensation is soon developed.

Considerable prominence has now been given to the observation that the daily intake of carbohydrate is a factor of considerable importance in determining the nature of the response to extract of the anterior lobe of the pituitary. Some of the experimental work of other investigators is of considerable interest in this connection and it is profitable to review their findings and conclusions at this time. As a general rule comparatively little attention has been paid to the composition of the diet of the experimental animals treated with anterior pituitary extract but some workers have made a special study of this factor.

Reference has already been made to the attractive hypothesis advanced by Himsworth that insulin is secreted by the pancreas in a physiologically inactive form, and that this form is converted into active insulin by an activator, called 'insulin kinase', believed to be produced by the liver. The increase in carbohydrate tolerance and in insulin sensitivity following a high carbohydrate diet was explicable on the basis that the administration of carbohydrate stimulated production of insulin-kinase. This hypothesis of Himsworth was largely based on blood sugar curves and there was no direct evidence advanced of the existence of insulin-kinase in liver tissue. Originally this conception of the effect of a high carbohydrate diet in increasing glucose tolerance was based on the idea that when such a diet was being consumed the efficiency/

efficiency of insulin was increased, insulin being activated by an insulin-kinase. At the same time Himsworth recognised that his results were equally explicable on the grounds of the removal of an inhibitor of the action of insulin. Although the idea of the existence of such an inhibitor seemed less probable at the time that the hypothesis was originally put forward, the later recognition that the anterior pituitary was capable of secreting a substance having the property of diminishing, or even abolishing the action of insulin, caused Himsworth to investigate the problem from another angle. In the words of Parsons (1938): "Himsworth with the help of McNair Scott proceeded to strangle the infant to which he had given birth."

Himsworth and Scott (1938a) studied the effect of the low and the high carbohydrate diet in rabbits in which the hypophysis had been removed. Their results showed that the changes in glucose tolerance and insulin sensitivity normally brought about in rabbits by altering the carbohydrate content of the diet are abolished in the absence of the pituitary. Furthermore, in hypophysectomized rabbits receiving a high carbohydrate diet the injection of anterior pituitary extract results in an impairment of sugar tolerance and insulin sensitivity similar to that occurring in the intact animal on a low carbohydrate diet. These observations encouraged Himsworth and Scott to suggest that the reduction in sugar tolerance and insulin sensitivity resulting from a low carbohydrate diet are better explained by an increased secretion of the 'anti-insulin' substance from the pituitary rather/

rather than by the action of an activator.

From the point of view of the present investigation this conclusion of Himsworth and Scott is of great interest. All the evidence advanced has been to show that anterior pituitary extract tends to increase sugar tolerance if the administration is continued for a sufficient period of time, that is to say the glucose tolerance curves ultimately resemble those obtained from subjects taking a high carbohydrate diet; but according to Himsworth and Scott the diminished tolerance seen when a low carbohydrate diet is taken is due to stimulation of the anterior lobe of the pituitary. The findings of the present writer are therefore directly opposed to those of Himsworth and Scott for, if this hypothetical stimulation of the anterior pituitary occurs, the result should be an ultimate increase in sugar tolerance, according to the conclusions previously formulated. The results obtained by injecting anterior pituitary extract in experimental animals also gives little support to the conclusions of these workers since it has been repeatedly demonstrated that the injection produces only a temporary hyperglycaemia which soon disappears even although the injections are continued (Baumann and Marine, 1931; E.I. Evans, 1933; Young, 1936; Houssay, 1937; Long, 1937), and it has been noted by E.I. Evans that injection of anterior pituitary extract in dogs causes a hyperglycaemia which disappears after a period of about one week and is replaced by subnormal blood sugar levels. The explanation of this difference might be due to a difference in the total quantities of extract,/

extract, injected in the one example, and secreted in the other, for it is most likely that the pancreas might be overwhelmed by the action of large amounts of extract, this has indeed been shown to occur by Young (1937), but when it does happen a permanent diabetes develops and not a physiological diminution in tolerance. It might be justifiably argued that in acromegaly there is frequently observed a diminution in glucose tolerance almost certainly the result of oversecretion of the anterior pituitary, but can one say that the disturbance of carbohydrate metabolism seen in this disease has a similar basis to the changes seen in the normal physiological response to a low carbohydrate diet? Especially when there exists a fairly satisfactory explanation based on the assumption that there is a diminution in insulin production under these circumstances.

There is another point on which the difference of opinion is obvious: according to Himsworth and Scott the loss of glucose tolerance which occurs when a low carbohydrate diet is being taken is the result of an oversecretion of the anterior lobe of the pituitary. However in the present investigation it has been shown that if anterior pituitary extract is injected while the subject is taking such a diet an increase in glucose tolerance occurs: this result is the opposite of what would be expected according to the hypothesis of Himsworth and Scott, since under these circumstances the injections would aggravate an existing over-secretion of the anterior lobe of the pituitary and produce a further decrease of sugar tolerance.

It has been suggested (Himsworth and Marshall, 1935) that, contrary/

contrary to general belief, the diet of diabetics before the onset of the disease is relatively low in carbohydrate, and that the incidence of diabetes is low in these countries where a high carbohydrate diet prevails, and high in countries where low carbohydrate are taken. If the taking of a low carbohydrate diet can be shown to stimulate the pituitary gland to oversecretion then an attractive explanation for this observation would be provided (Himsworth and Scott, 1938a); but experimental results provide little hope that proof of this will be obtained. Houssay (1937) and Long (1937) have pointed out that the diabetogenic properties of anterior pituitary extract are only seen in normally fed animals, and hyperglycaemia does not occur, or only to a slight degree, if the animals are fasted; on the other hand the hyperglycaemia is more rapid and intense if a high carbohydrate diet is given. This observation agrees well with the conclusions reached in the present investigation and therefore there seems little need to reject them even after giving careful consideration to the apparently contrary findings of Himsworth and Scott.

There is of course no desire to ignore the interesting observations of these workers but it is difficult to reconcile them both with the present findings and with those of other investigators obtained with experimental animals. It is possible that the cause of the apparent difference of opinion is due to the fact that Himsworth and Scott were using not a crude extract, as in the present study, but one fraction of the extract of the pituitary, but it is impossible to assess the importance of this difference in technique. Another, and possibly more

valid explanation, is that Himsworth and Scott were thinking in terms of <u>secretion</u> of the anterior pituitary such as might normally occur, whereas the others quoted were drawing their conclusions from the effects of <u>injection</u> of the extract. It is evident that there might be a considerable difference between the effects of a relatively large amount injected in a short space of time and the action of a small amount secreted over a longer period. Here may lie the explanation, but it is customary to draw conclusions concerning the physiological action of one of the endocrine glands by observing the effects produced by injection of an extract obtained from it, and it is not intended to enter into a philosophical discussion on the rights and wrongs of such a procedure, nor to depart from the practice in this investigation.

Table 12.

Temporary Failure of Carbohydrate Tolerance on changing to a High Carbohydrate Diet.

Case.	Carbohydrate Allowance.	Time.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise in mg/100 c.cm.
96.	50 gm.	0	105	176	286	263	208	
	500 gm.	7 days.	100	200	286	322	250	36
		17 days.	80	143	156	122	90	
97.	50 gm.	0	84	172	250	175	125	
	500 gm.	7 days.	82	178	379	217	178	129
		17 days.	76	146	134	102	86	
99.	50 gm.	0	95	135	149	143	110	
	500 gm.	7 days.	110	185	196	145	123	47
		14 days.	80	126	124	104	123	
101.	50 gm.	0	94	122	156	169	139	
	500 gm.	7 days.	73	161	264	302	179	133
		17 days.	82	163	130	105	93	
Mean:			94	151	210	187	145	
			91	181	281	246	182	
			79	144	136	108	98	

Table 13.

The Effect of Continued Administration of Anterior Pituitary Extract while a High Carbohydrate Diet was being taken.

Case.	Age.	Sex.	Disease.	Total Amount of Extract.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
105.	24 yr.	F.	Acute Rheumatism.	0	78	116	137	151	118	
				3 c.cm.	70	130	212	185	175	+61
				6 c.cm.	64	97	144	135	115	-68
106.	41 yr.	F.	Disseminated Sclerosis.	0	92	189	185	137	106	
				3 c.cm.	94	179	218	169	111	+29
				6 c.cm.	84	132	161	152	95	-57
107.	54 yr.	F.	Peptic ulcer.	0	79	178	161	154	118	
				3 c.cm.	82	172	159	125	89	-6
				6 c.cm.	73	139	116	77	72	-33
108.	32 yr.	F.	Influenza.	0	92	166	172	103	65	
				3 c.cm.	83	147	182	135	67	+10
				6 c.cm.	71	133	74	72	58	-49
109.	41 yr.	F.	Pernicious Anaemia.	0	89	179	103	71	66	
				3 c.cm.	97	228	159	78	74	+49
				6 c.cm.	75	143	125	78	49	-85
110.	13 yr.	M.	Acute Rheumatism.	0	69	128	108	97	99	
				3 c.cm.	92	133	108	103	94	+5
				6 c.cm.	93	169	149	114	86	+36
				10 c.cm.	79	161	118	94	82	-8

Table 13. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
111.	55 yr.	M.	Inguinal Hernia.	0	87	152	138	127	97	
				3 c.cm.	111	208	203	150	144	+56
				6 c.cm.	93	178	168	112	106	-30
Mean:					84	158	143	120	96	
					90	176	183	137	107	
					77	140	129	103	82	

Table 14.

The Effect of Continued Administration of Posterior Pituitary Extract while a High Carbohydrate Diet was being taken.

Case.	Age.	Sex.	Disease.	Total Amount of Extract.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
112.	67 yr.	F.	Renal Calculus.	0	75	156	148	124	86	
				1.5 c.cm.	78	178	183	168	112	+27
				3.0 c.cm.	82	176	180	156	122	-3
113.	35 yr.	M.	Septic foot.	0	89	143	133	125	92	
				1.5 c.cm.	83	196	173	127	112	+53
				3.0 c.cm.	80	145	169	137	104	-25
114.	67 yr.	F.	Osteo-arthritis.	0	73	141	114	102	100	
				1.5 c.cm.	86	159	134	101	97	+18
				3.0 c.cm.	78	185	179	133	94	+26
115.	54 yr.	F.	Pernicious Anaemia.	0	74	111	116	125	112	
				1.5 c.cm.	85	147	169	103	83	+44
				3.0 c.cm.	88	121	161	104	86	-8
116.	60 yr.	F.	Peptic ulcer.	0	86	147	161	115	101	
				1.5 c.cm.	69	204	131	79	70	+43
				3.0 c.cm.	71	154	134	122	70	-50
117.	48 yr.	M.	Peptic ulcer.	0	73	94	139	89	57	
				1.5 c.cm.	78	134	143	147	84	+8
				3.0 c.cm.	80	147	102	92	49	nil.
118.	47 yr.	F.	Peptic ulcer.	0	73	128	104	40	52	
				1.5 c.cm.	70	135	100	50	63	+7
				3.0 c.cm.	79	189	141	116	84	+54

Table 14. (Contd.)

Case.	Age.	Sex.	Disease.	Total Amount of Extract.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
119.	47 yr.	F.	Acute Rheumatism.	0	79	139	185	105	90	
				1.5 c.cm.	90	145	179	136	169	+11
				3.0 c.cm.	74	112	134	189	122	-7
120.	48 yr.	F.	Disseminated Sclerosis.	0	88	161	154	130	114	
				1.5 c.cm.	92	175	166	154	116	+14
				3.0 c.cm.	69	128	151	94	92	-24
Mean:					79	136	139	106	89	
					81	181	153	145	101	
					78	136	150	127	91	

Section Ten.

The Endocrine Control of the Blood Sugar Level.

During the experiments dealing with the effect of the low carbohydrate diet an interesting observation was made. It is generally admitted that the effect of such a diet is the production of a decrease in glucose tolerance, and the curves presented in these experiments were taken as illustrating this finding. Agreement on this point is so universal that it was not thought worth while estimating the glucose tolerance of the patients before giving them the low carbohydrate diet in order to demonstrate that a diminution actually occurred. Accordingly, although there is no actual proof that tolerance had been diminished as the result of this procedure, it may be accepted with confidence that this actually occurred; but a consideration of the figures presented make it apparent that there is a considerable variation in the degree of diminution of sugar tolerance produced in this way. It is this finding that arouses some interest.

In Table 15 are summarized the blood sugar curves obtained from the 17 cases who were subjected to the low carbohydrate diet; in Fig. 15 are plotted the blood sugar values of 17 curves obtained under these circumstances. Also in Fig. 15 are 2 composite blood sugar curves made up of the highest values recorded in the group in the one instance, and the lowest recorded in the other.

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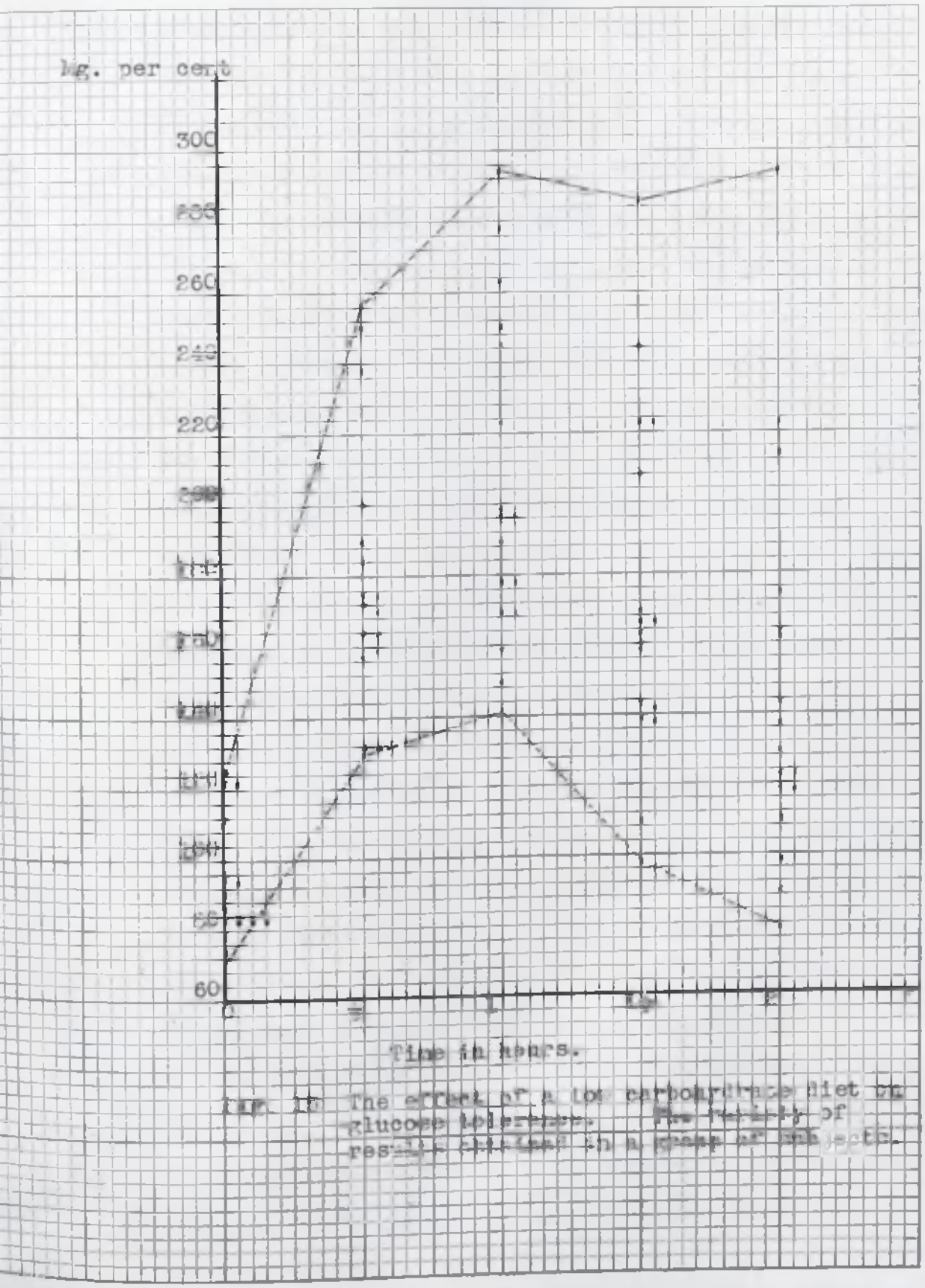

Fig. 11 The effect of a low carbohydrate diet on glucose tolerance. The result of [illegible] results obtained in a case of [illegible]

A consideration of this figure makes clear the great differences existing in the blood sugar curves recorded while the subjects were taking a diet poor in carbohydrate. A study was made of the factors that might be responsible for such a wide variation in response to a stimulus regarded as being identical in each case.

As in the previous sections the numbers examined were too small to permit of any differences in age or sex being taken into account, or for that matter of any gross differences that might distinguish one subject from another. With these reservations the cases were regarded as identical and attention was directed towards the discovery of less obvious factors that might be responsible. It has been mentioned before that a period of one week during which the low carbohydrate diet was given was too short to allow of the individual accustoming himself to the unusual circumstances. In other words it might be said that if a longer period of time had been allowed those cases which showed little sign of any decrease in glucose tolerance would ultimately have given higher blood sugar curves as the period of carbohydrate starvation was prolonged. This may well be true but it does not alter the fundamental fact that a reduction in the carbohydrate intake for one week caused a great diminution in sugar tolerance in some cases, and only a slight diminution in others.

Now, as has been previously stated, it is generally agreed that the cause for the diminished sugar tolerance seen when a low carbohydrate diet is being taken is the absence of any active stimulation of the pancreas to secrete insulin. Under these

circumstances/

circumstances there is no difficulty in explaining the high blood sugar curves which were obtained in some of the cases; but it is difficult to understand why some of the glucose tolerance curves obtained under what were intended to be identical conditions did not show this diminution in tolerance. In these last cases there did not seem to be any great deficiency of insulin despite the consumption of a diet poor in carbohydrate, so far as could be judged from the manner in which they reacted to 50 gm. of glucose taken by the mouth. Therefore it would appear that the answer must be sought by considering the mechanism of insulin secretion, since the existence of a stimulus of this mechanism other than a plentiful supply of carbohydrate in the diet would provide an explanation.

The opinion of the Houssay school (Houssay, 1937) that the control of insulin secretion is mainly a humoral process, the level of the blood sugar regulating the output of insulin, and that the part played by the nervous system is secondary and can be dispensed with, has already been stated. This is however not universally accepted and there are others who maintain that the control of insulin secretion by the central nervous system through the vagus is of prime importance. Prominent amongst those who hold the latter view are La Barre and his associates who have advanced evidence from cross-circulation experiments in dogs (La Barre, 1933) that the secretion of insulin is under the control of the vagus centre, which depends for its stimulation on the

blood/

blood sugar level. Whether the mechanism is humoral or nervous is of no present importance; what is important is that there is agreement that the blood sugar level is ultimately responsible. The position might be summed up by saying that when an abundant supply of carbohydrate is entering the circulation sugar tolerance is high; when a small amount of carbohydrate is entering the circulation sugar tolerance is low. It would seem therefore that the existence of some other source of carbohydrate would provide an explanation for the finding that some individuals did not show any appreciable loss of sugar tolerance when taking a low carbohydrate diet.

In the absence of a plentiful supply of carbohydrate in the diet it is difficult to conceive of any other source of carbohydrate. The formation of carbohydrate from the dietary protein might be of importance in this connection, but it has been shown (Himsworth, 1935) that the amount of protein in the diet is of no importance in determining the glucose tolerance and so this possibility can be ignored. For the same reason any possible formation of glucose from fat can be rejected as an explanation. A factor that cannot be directly assessed but which may be of importance is the quantity of glucose discharged into the blood stream from endogenous sources; it is obvious that this must play a part in the stimulation of insulin production since there is no apparent difference between glucose absorbed from the alimentary canal, and glucose discharged into the blood stream from the liver, but this possibility has evidently been ignored by the majority of workers.

The use of extracts of the anterior and posterior lobes of the pituitary in conjunction with a low carbohydrate diet in the present investigation has shown that, when these extracts were injected, the loss of tolerance which usually resulted from the consumption of such a diet was made less obvious. It was suggested that the increase in the amount of glucose in the blood following the injection of these extracts was apparently capable of compensating for the diminished quantity of glucose entering the circulation from dietary sources, at least as far as the maintenance of normal glucose tolerance was concerned. The production of a hyperglycaemia is however not the only action on carbohydrate metabolism produced by pituitary extracts, and it cannot be argued solely from their use that an endogenous hyperglycaemia can compensate for a reduction in dietary carbohydrate by preventing loss of sugar tolerance. For this purpose it is necessary to produce an endogenous hyperglycaemia without at the same time introducing other actions on the metabolism of carbohydrate, such as occur when pituitary extracts are used. In other words it seemed necessary to establish whether the production of a hyperglycaemia by the regular injection of adrenalin could take the place of the normal post-prandial hyperglycaemia so far as the stimulation of the mechanism of insulin production was concerned.

Method. Seven subjects were chosen in the same way as in previous experiments and were given the diet containing a daily allowance/

allowance of only 50 gm. carbohydrate for a period of one week. At the end of this period of time adrenalin hydrochloride 1:1000 solution was injected twice daily in doses of 0.3 c.cm. for 3 days. Blood sugar curves were carried out before and after the use of adrenalin.

Results. In all cases the result of the administration of adrenalin was an increase in sugar tolerance as shown by a lowering of the blood sugar levels. These results are summarized in Table 16 and Fig. 16.

Discussion. The purpose of the experiment just described was to ascertain whether the amount of glucose discharged into the blood stream from endogenous sources was as active as glucose absorbed from the alimentary canal in influencing the carbohydrate tolerance; and also to determine whether the state of activity of one or other of the endocrine glands might provide an explanation for the extraordinarily variable blood sugar curves obtained, when a group of individuals were subjected to the same restriction of carbohydrate intake. In this latter connection it may be noted that the blood sugar curves obtained from this group of patients after a period of one week on a low carbohydrate diet showed the same wide individual differences that had been noticed in the other groups. The results obtained provide convincing additional evidence that a hyperglycaemia from endogenous sources is capable of replacing some of the dietary carbohydrate so far as the maintenance/

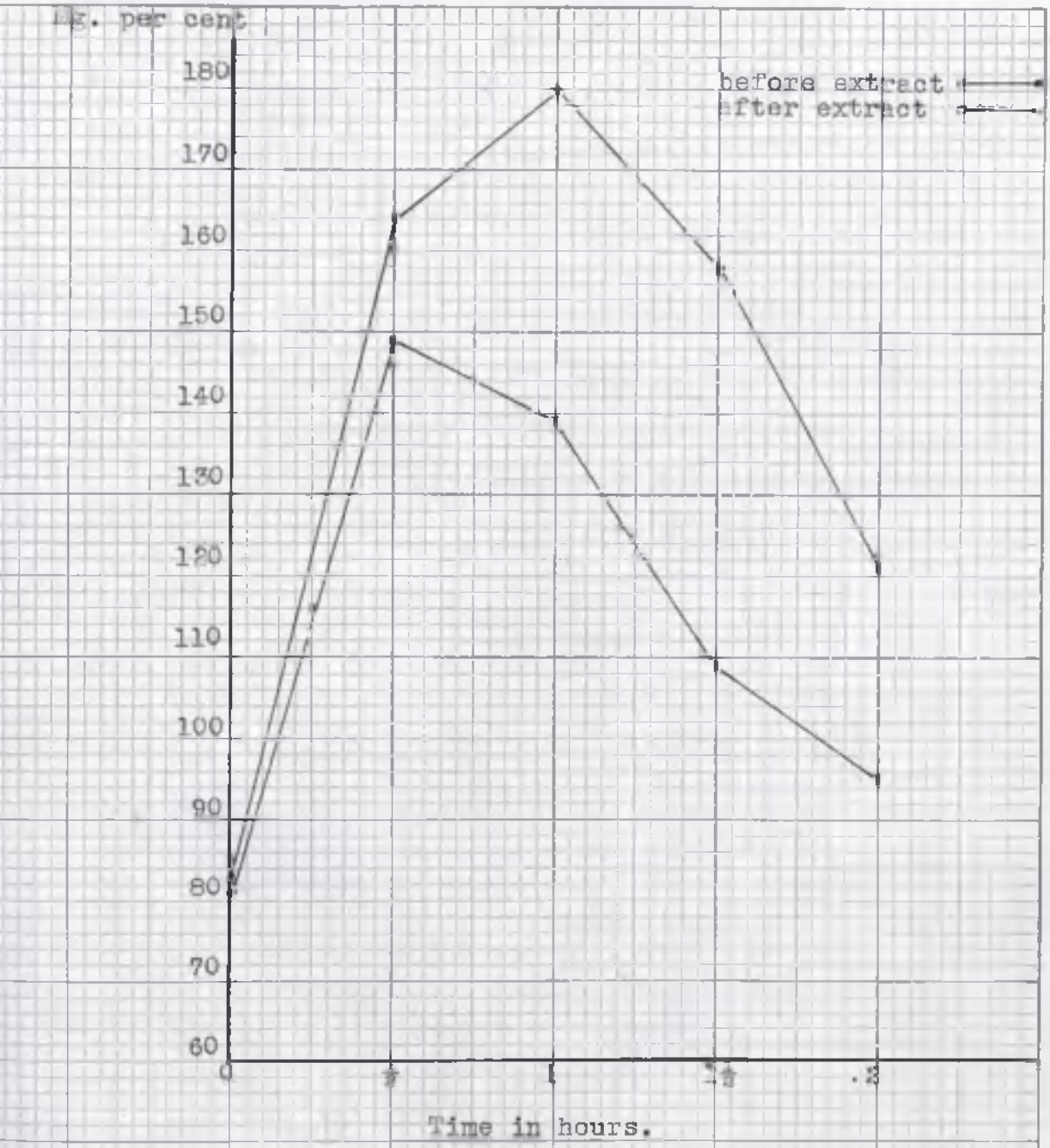

Fig. 16 Effect of injection of adrenal medullary extract when a low carbohydrate diet is being taken.

maintenance of glucose tolerance is concerned, and it is submitted that this point has been proved. If this is accepted it is not difficult to extend the principle and so provide an explanation for the fact that certain individuals as compared with others show little decrease in glucose tolerance when subjected to a restriction of carbohydrate. It has been emphasized that it is the level of the blood sugar that regulates the secretion of insulin, whether this is done by a humoral or by a nervous mechanism is not of present importance, a reduction in carbohydrate intake therefore leads to a reduction in insulin production which is shown by a rise in the blood sugar curve; but in some cases this rise in the blood sugar values is not seen therefore it is reasonable to look for another source of carbohydrate than that in the diet. Since gluconeogenesis from dietary protein or fat cannot provide the explanation the only other possible source of carbohydrate is that stored in the tissues, and a discharge of glucose from this source might well be expected to stimulate insulin production. When it is realized that the ability of a release of glucose from endogenous sources to compensate for a reduction in dietary carbohydrate has been proved, this assumption is by no means unreasonable.

The conception underlying the foregoing arguments is that the effect of an injection of an endocrine extract cannot be explained wholly by considering the known action of the particular extract alone, but may involve a consideration of the action of

its antagonists. The action of adrenalin provides a simple example. Adrenalin having the action of causing a hyperglycaemia is generally considered as contra-insular in its effect, and so it might be concluded that a diminution in glucose tolerance would result from its continued use. This view however takes no cognisance of the fact that hyperglycaemia is the stimulus for insulin secretion, and accordingly an outpouring of adrenalin is followed by an increased production of insulin, the final result being, as has been shown during the course of experiments which have been recorded in this communication, a gain in sugar tolerance. It is not suggested that this viewpoint is entire novel, but it is maintained that too little attention has been paid to it in theoretical considerations involving the roles of the various endocrine organs in the regulation of carbohydrate metabolism, and most particularly in studies concerned with the explanation of clinical disorders of the control of the blood sugar. In these fields attention has been too long directed to the action of one particular secretion without any consideration of the possible effects of the reaction of other organs.

The general attitude adopted by clinicians towards these problems may be summed up by quoting from a popular text book (Tidy, 1934): "Four ductless glands influence the amount of sugar in the blood, viz.: (a) Diminish: pancreas. (b) Increase: suprerenals, pituitary, and thyroid." That this statement is true of the immediate action of these glands is not denied, but it

is not only the immediate reaction which follows the outflow of these secretions that is of importance, the remote effects involving the response of the tissues to their influence is of as great if not greater importance. The immediate effect of glucose taken by the mouth is an increase in the blood sugar level, and yet in the long run the ingestion of glucose ultimately produces a lowering of the blood sugar by stimulating insulin production. Conversely, a reduction in the carbohydrate intake causes in the end a rise in the blood sugar, on account of the defective production of insulin. In this example the immediate effect of glucose is ultimately reversed on account of the action of its antagonist, insulin. Similarly it is argued that any extract capable of increasing the quantity of sugar in the blood will by so doing provoke a response on the part of the pancreas, and so ultimately the blood sugar level will be lower than it was in the beginning. Of course it must be realized that this improvement in glucose tolerance may be masked in certain instances by some associated action, such as the production of a state of insulin resistance.

The view that has been expressed above is one obviously much more likely to provide a satisfactory explanation of the process of control of the blood sugar level, than that generally expressed by clinicians which tends to explain a complicated biological action as if it were an experiment <u>in vitro</u>, and it is not easy to understand why the simpler explanation has been accepted for so long. The writer was led to conclude from a study of the literature that its origin was to be found in the work of Cushing (1911). Cushing and his colleagues found that hypophysectomy/

hypophysectomy in experimental animals resulted in an increase in glucose tolerance, and it was subsequently observed that patients suffering from unmistakable hypophyseal deficiency, associated with destructive pathological processes similarly showed a high tolerance for sugar. Since, in their opinion, acromegaly and gigantism were expressions of an overactive pituitary it would be expected that hyperglycaemia and glycosuria would be common clinical findings in these conditions. These features, were found to be frequently present in acromegaly and other conditions due to hyperpituitarism, but not invariably so; indeed in the majority of sufferers from this complaint a high sugar tolerance was found. This led to the conception that when a high sugar tolerance was found it could be concluded that the individual was passing from a state of increased glandular activity to one of lower activity. Indeed it was stated that the strongest argument in favour of the hypothesis that in acromegaly there was a tendency for the disease to change from hyper- to hypopituitarism, was this observation that in certain cases a change from diminished to increased glucose tolerance might be noticed. Along these lines developed the idea that overaction of the pituitary could be recognised by the low sugar tolerance, and underaction by the presence of increased tolerance.

When the evidence on which the Cushing hypothesis is based is examined it is seen that the disappearance of glycosuria and sometimes of frank diabetes mellitus in cases of acromegaly has been noted on many occasions (Colwell, 1927). This is explained

by/

by a change occurring in the acromegalic process so that the pituitary gland which was originally overactive becomes eventually underactive; and this leads to a consideration of the carbohydrate tolerance in clinical cases to hypopituitarism. There has been general agreement that an increased sugar tolerance occurs in such cases: Langdon-Brown (1936) states that sugar tolerance is increased in the Fröhlich syndrome, at least in the later stages, and goes on to say that this might be expected, since the principles secreted by both lobes of the pituitary which are antagonistic to insulin are deficient. There have however been observations to the contrary: John (1925) reported 5 cases of hypopituitarism, one of these suffered from severe diabetes, one from mild diabetes, and in the remaining 3 cases the blood sugar curves were suggestive of a pre-diabetic condition; Wilder and Sansum (1917) observed that blood sugar curves following the intravenous injection of glucose gave normal figures and accordingly sugar tolerance was not increased in hypopituitarism.

The observation that removal of the hypophysis in experimental animals resulted in increased carbohydrate tolerance has already been recorded (Cushing, 1911) but the results of later workers obtained after hypophysectomy are at first sight conflicting. Removal of the hypophysis in dogs has been found to cause an increase in glucose tolerance (Houssay and others, 1922; Kepinov, 1934a, 1934b; Mahoney, 1934), and a similar result has been observed in the case of the rabbit (Corkill and others, 1933); on the other hand Camus and Roussy (1920) found that partial

removal of one or both lobes, or total removal of the whole gland did not appreciably modify carbohydrate tolerance in dogs, and Colwell (1927) noted that the response of the hypophysectomized dog to intravenous injection of glucose was normal. Other workers found hypophysectomy in dogs produced a diminution in glucose tolerance as judged by the course of the blood sugar following intravenous glucose injection (Daggs and Eaton, 1933; Biasotti, 1934c), and Russell and Cori (1937) came to the conclusion using rats from which the hypophysis had been removed. The probable explanation for these conflicting results is that removal of the hypophysis is followed by a reduction in absorption from the intestine (Phillips and Robb, 1934; Bennett, 1936; Samuels and Ball, 1937), and this probably accounts for the apparent increase in glucose tolerance as judged by the height of the blood sugar curve. Therefore evidence concerning the carbohydrate tolerance of the hypophysectomized animal can only be secured from intravenous glucose tolerance curves, in order to avoid the factor of diminished intestinal absorption. If only results from these experiments are considered the balance of opinion is in favour of the existence of a <u>diminished</u> sugar tolerance as the result of hypophysectomy.

It can now be appreciated that there is by no means a secure foundation for the hypothesis of Cushing concerning the carbohydrate tolerance in hypopituitarism, either on clinical or experimental grounds, and when attention is directed towards hyperpituitarism little more experimental or clinical support is perceived./

perceived. Reference has already been made to the experiences of many workers on the ultimate result produced by the continued administration of anterior pituitary extract to laboratory animals, and it has been pointed out that until recently there has been almost universal agreement that the hyperglycaemia produced in this way was temporary in nature, and disappeared even if the injections were continued. In 1937 Young was able to overcome this apparent resistance to anterior pituitary extract by giving large doses up to the equivalent of 35 gm. of fresh gland substance to dogs, and so producing a permanent diabetic state. This work has been confirmed (Young, 1938; Campbell and Best, 1938) but apart from these and similar experiments involving the use of massive doses of extract, no attempt has been successful in producing a lasting diminution in glucose tolerance by this means. It is interesting to note that when the resistance of the pancreas is broken down in this way the result is the production of diabetes and not merely a decrease in sugar tolerance, such as might be expected from the Cushing hypothesis. There is also some histological evidence that the pancreas is capable of compensating for any pituitary overactivity. Richardson and Young have shown that the injection of anterior pituitary extract results in islet tissue hyperplasia in the rat (1937) and also in the dog (1938). In the clinical field Simpson (1936) in his summary of the features of acromegaly notes the occurrence of occasional hypertrophy of the islets of Langerhans, and states that this may be evidence of

functional/

functional antagonism to the pituitary diabetogenic substance.

In connection with this hyperplasia of the islet tissue as evidence of a compensatory reaction on the part of the pancreas the interesting case published by Lloyd (1929) is worthy of mention. The patient was a female, aged 22 years, who developed clinical signs of a pituitary tumour from which she eventually died. At autopsy a malignant hypophyseal adenoma was discovered but the main interest in the case was the discovery of 10 adenoma-like nodules of islet cells in the pancreas. Hyperplasia of the parathyroids was also noted. According to Lloyd it seemed more than probable that these changes were related, but there was insufficient evidence to draw a definite conclusion on this point. There were no clinical indications for the estimation of the blood sugar or calcium levels, and in the absence of these observations there is no means of determining whether the tumour-like pancreatic and parathyroid tissue had any functional activity. However when the case is reviewed along with the findings of Richardson and Young (1937, 1938), to which reference has already been made, there can be little reasonable doubt that the pancreatic adenomata represent a response to pituitary overactivity. More than this cannot be said in the unfortunate absence of biochemical findings.

From this short review of the literature it can be concluded that it is not possible to determine the degree of pituitary activity simply by estimating the carbohydrate tolerance in any particular case, since the carbohydrate tolerance is not simply the/

the result of any under- or overactivity of the pituitary alone, but is the sum of the action of the pituitary and the pancreas. This statement should be regarded as tending to simplify the problem overmuch, and the possibility that other endocrine glands also play their part is by no means disregarded.

It has been remarked that there is no intention to present this viewpoint as entirely novel, but a study of the literature makes it evident that surprisingly little work has been carried out and presented as demonstrating the close interrelationship between the various endocrine organs and their antagonists in the control of the blood sugar level. A relationship of a sort has of course been a fundamental conception underlying all hypotheses concerning the control of the blood sugar level, but it has usually been expressed in terms of the unopposed action of one particular secretion, for example: "Hyperglycaemia and glycosuria are, therefore, produced by increased secretion of the thyroid, of the suprarenal medulla, or of the posterior lobe of the pituitary, and by deficiency of the pancreatic secretion. Increased sugar tolerance, on the other hand, is produced by deficiency in the secretion of the first three glands" (Clark, 1933). The origin of this simple hypothesis has been traced to what appears to be its source and the validity of the clinical and experimental evidence advanced in its favour has been criticised.

The work of Corkill (1930) presents a striking contrast to that previously mentioned. This worker observed that the injection of adrenalin in quantities too small to cause glycosuria produced in young fasting rabbits a change in the glycogen distribution, closely resembling that following the injection of

insulin/

insulin. Conversely, it was suspected from the effect of insulin injection that the action of insulin itself was complicated by that of adrenalin secreted in response. He concludes that it is doubtful whether the whole of an effect following insulin injection into any normal animal can be attributed to insulin alone. In support of this work of Corkill the observations of Riddle and others (1924) may be noted; these workers found that the administration of large doses of insulin to pigeons caused enlargement of the adrenal glands. This is in agreement with Gohar (1933) who found that repeated doses of insulin when given to rats causes an increase in the weight and adrenalin content of the adrenals.

Other workers have also endeavoured to show that the effect of injection of an endocrine substance cannot be explained solely in terms of the action of the particular extract injected. Prominent among these are La Barre and his colleagues (1933) who have shown by means of cross-circulation experiments that the injection of adrenal and pituitary extracts into the donor animal is followed by a fall in the blood sugar of the recipient, and this is regarded as evidence that adrenalin and pituitary extract stimulate the secretion of insulin. The work of Richardson and Young in demonstrating that the injection of anterior pituitary extract is capable of causing proliferation of the islet cells in the pancreas of the rat (1937) and the dog (1938), may be taken as demonstrating a similar observation in another manner. Another aspect of the problem was profitably studied by Marks and Young (1939)/

(1939) when they demonstrated that the amount of insulin present in the pancreas of the rat was greatly increased as the result of injection of anterior pituitary extract.

From the study of findings such as have been mentioned it is concluded that it has long been recognised by certain physiologists that the injection of an endocrine extract produced effects which were the sum of the action of the original extract and that of its antagonists, and could not be explained on the basis of the unopposed action of one substance. It is however evident that comparatively little attention has been paid to this when attempts were made to explain clinical disorders of blood sugar control, and errors have consequently been made in their interpretation. A good example of the manner in which such errors might arise was provided in one instance. Case 128, a male aged 15 years, was admitted to the Western Infirmary suffering from a fracture of the femur. He was obviously grossly overweight for his age and height but could not be weighed on account of the fractured femur. The general appearance was suggestive of the Frohlich hypoplasia, but somnolence was not a feature of the case. It was decided to estimate the glucose tolerance and the following result was obtained:

Fasting	81	mg./100 c.cm.
½ hour	192	" "
1 hour	141	" "
1½ hours	124	" "
2 hours	74	" "

This result showed no evidence of increased glucose tolerance, and indeed it might be said that the tolerance was rather less than would be expected in a boy of his age. As a matter of

interest/

interest it was decided to try the effect of giving anterior pituitary extract over a considerable period, and accordingly one c.cm. was given daily for a period of 12 days. At the end of this time the sugar tolerance was again estimated with the following result:

Fasting	68	mg./100	c.cm.
½ hour	112	"	"
1 hour	96	"	"
1½ hours	88	"	"
2 hours	69	"	"

(These findings are shown in Fig. 17.)

This second curve differs considerably from the previous one and now there is no doubt that the sugar tolerance is high. Furthermore if any importance is placed on the diagnostic value of a low blood sugar curve in hypopituitarism this second curve might be regarded as typical of that condition. Therefore the second blood sugar curve obtained from this case supports the diagnosis of underactivity of the pituitary; but this curve was secured only after the injection of anterior pituitary extract over a period of 12 days, in other words, after a period when there was an excess of pituitary secretion in the circulation. It is considered that this gives a good example of the danger in drawing conclusions concerning the degree of activity of the pituitary from the state of carbohydrate tolerance alone, without taking into consideration the response made by the opposing gland.

From the foregoing discussion it is concluded that there is ample evidence that the physiological control of the blood sugar level cannot be explained by a consideration of the action of one or/

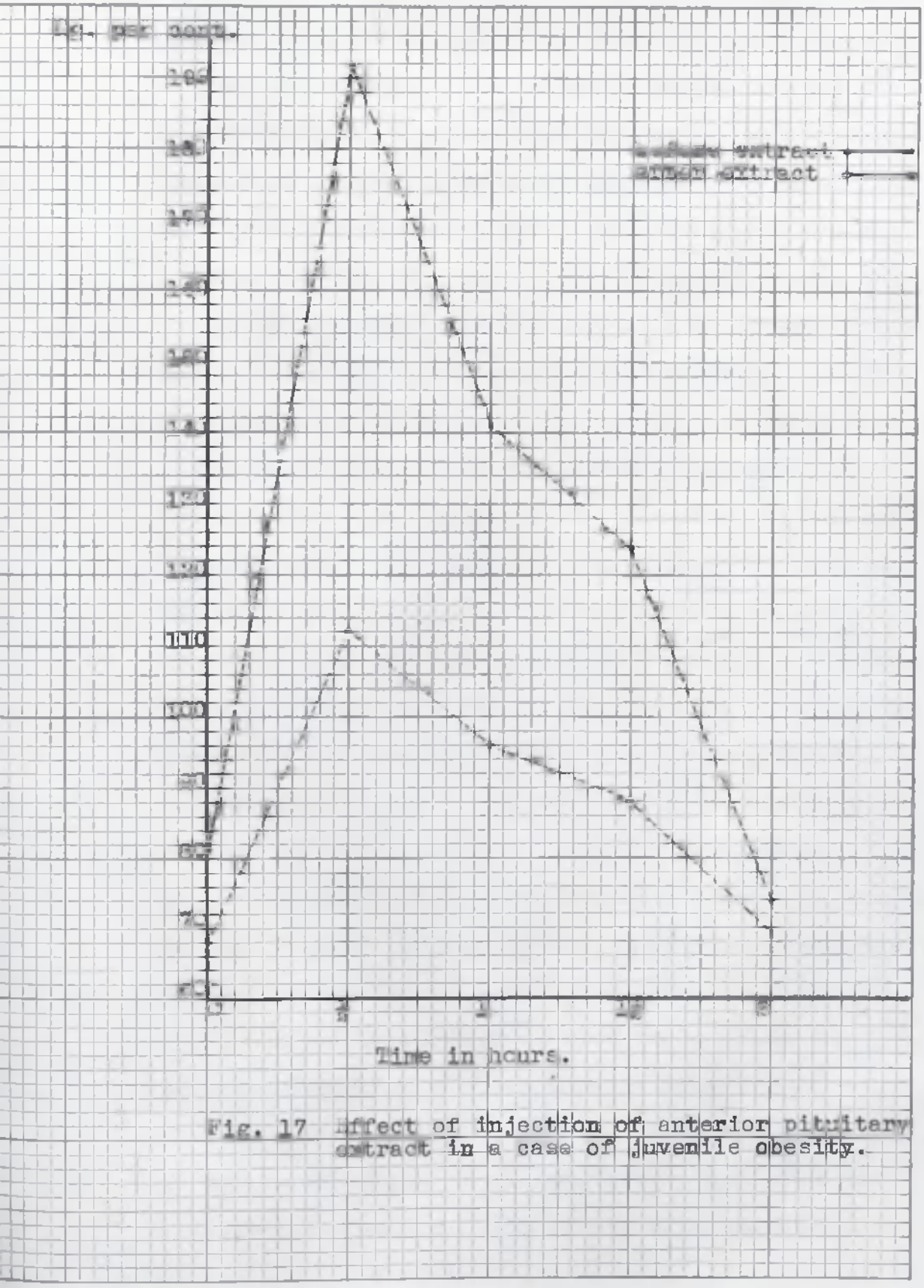

Fig. 17 Effect of injection of anterior pituitary extract in a case of juvenile obesity.

or other gland, but that the action of the antagonists must also be taken into account. This has been demonstrated in the results obtained in the present investigation, as well as in the experimental observations of others, but this is by no means the only factor to be considered even if the parts played by other organs such as the liver, and possibly the central nervous system, are excluded from the present discussion. From the experiments which have been outlined it is easy to understand that overactivity of a gland secreting a hyperglycaemic substance can cause a decrease in glucose tolerance; but if this action is persisted in the ultimate effect is to increase glucose tolerance.. It has also been shown that in the presence of a large intake of carbohydrate the hyperglycaemic properties of certain extracts are enhanced; and a low carbohydrate diet may mask the presence of hyperglycaemic substances in the blood stream so that they could not be detected by examining the blood sugar curve. When the production of contra-insular hormones is less than usual an increase in glucose tolerance may be found, but only if the supply of insulin is kept up. If this is diminished in the absence of hormones stimulating the islet tissue of the pancreas then no alteration in tolerance need be expected, and this is what probably would happen. No evidence has been presented as demonstrating that, when the production of contra-insular substances is defective, the taking of a high carbohydrate diet would tend to conceal their absence, but there is no valid reason why this should not be so and this supposition is indeed the logical outcome of the arguments which

have/

have been advanced.

It is also submitted that these same principles are effective in pathological conditions in which the blood sugar level is abnormal, and to explain the blood sugar curves obtained in these cases simply on the relative degree of activity of one or other gland must inevitably lead to faulty conclusions. It has been shown that experimental workers have long been aware of the existence of such a mechanism under both physiological and pathological conditions, but it is evident that clinicians have in general failed to appreciate this or to apply it to clinical problems.

[illegible]	[illegible]	[illegible]	[illegible]
95	130	[illegible]	143
[illegible]	[illegible]	[illegible]	141
122	175	[illegible]	169
[illegible]	172	141	[illegible]
[illegible]	159	138	[illegible]
[illegible]	165	173	[illegible]

Table.15.

The Effect of a Low Carbohydrate Diet on Glucose Tolerance.

	blood sugar mg./100 c.cm.				
Case.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.
88.	83	132	178	166	122
89.	95	164	149	139	119
90.	84	189	196	222	143
91.	79	132	159	160	137
92.	85	164	169	108	78
93.	73	157	245	222	214
94.	90	175	196	166	128
95.	83	184	189	138	108
96.	112	250	294	286	222
97.	72	200	263	208	175
98.	125	256	278	244	286
99.	95	130	169	143	122
100.	122	238	222	141	161
101.	122	175	250	169	163
102.	82	172	141	98	89
103.	84	159	198	159	98
104.	82	165	178	163	118

Table 16.

The Effect of Injection of Adrenal Medullary Extract when a Low Carbohydrate Diet is being taken.

Case.	Age.	Sex.	Disease.	Dose.	0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Fall in mg./100 c.cm.
121.	32 yr.	M.	Peptic ulcer.	0	78	149	175	185	122	
				1.8 c.cm.	75	161	115	95	86	-24
122.	36 yr.	M.	Disseminated Sclerosis.	0	86	238	232	147	105	
				1.8 c.cm.	87	212	166	106	63	-26
123.	40 yr.	F.	Anaemia.	0	88	147	154	179	137	
				1.8 c.cm.	91	156	122	112	110	-23
124.	28 yr.	F.	Acute Rheumatism.	0	80	143	169	156	128	
				1.8 c.cm.	75	112	137	94	87	-32
125.	56 yr.	F.	Bronchitis.	0	81	151	196	154	132	
				1.8 c.cm.	78	156	163	124	118	-33
126.	39 yr.	M.	Carcinoma of lung.	0	79	151	133	125	121	
				1.8 c.cm.	78	145	118	95	94	-6
127.	21 yr.	M.	Asthma.	0	87	172	204	157	116	
				1.8 c.cm.	82	103	151	137	104	-53
Mean:					83	164	180	158	121	
					81	149	139	109	95	

Section Eleven.

The Influence of Infection on the Response to Extract of the Anterior Lobe of the Pituitary.

In previous sections the relationship between the daily intake of carbohydrate and the response to anterior pituitary extract has been established. It has been shown that when a high carbohydrate diet was being taken the usual effect of the extract was to produce a diminution in sugar tolerance of a temporary character, but when the carbohydrate intake was low the usual effect was an increase in sugar tolerance. The connection between the amount of carbohydrate in the diet and the response to the extract was shown to be close, but was not absolute since exceptions to the general rule occurred. The presence of these exceptional cases suggested that the composition of the diet did not provide a wholly satisfactory explanation, and a careful consideration of the problem made it clear that other factors must be of importance.

The original problem was the difficulty in understanding why certain normal subjects should lose tolerance to glucose on being given anterior pituitary extract while others, apparently similar, should gain tolerance. The possibility was considered that an initial diminution in tolerance occurred in every instance but

was/

was only detected in a few, because only in these were glucose tolerance curves carried out at the most favourable time. This may explain some cases but cannot account for all as it was obvious that certain individuals required to be followed for a considerable period during which extract was given, before tolerance was seen to be regained. One difficulty in assessing the results that was recognised from the outset was that the subjects chosen for study were not normal, healthy individuals, but were either convalescent from the disease which originally required their admission to hospital, or were in such a condition at the time of examination that they could be reasonably regarded as in fairly good health. Although, as will be seen from a study of the results, there was no indication that any particular disorder was constantly associated with a particular type of response the possibility that the disease condition played the deciding part in determining the reaction of the subject cannot be ignored, and it must be clearly understood that there is no certainty that identical results would have been secured when dealing with perfectly normal individuals. This defect in the planning of the investigation however is one quite unavoidable in dealing with hospital material, and on account of the small numbers examined, its importance cannot be assessed unless by a consideration of factors likely to be operative in a number of the cases. Only one common factor could be examined when dealing with such a diversity of diseases, that of infection.

The presence or absence of infection is a matter of great

importance in evaluating blood sugar curves; Joslin (1935) goes so far as to say that the presence of an afebrile coryza is sufficient to cause a diminution in sugar tolerance. So far as obvious infection was concerned none of the cases examined were so affected, but it cannot be claimed that all were entirely free from infection of any kind, and since infection has long been known to be capable of diminishing sugar tolerance it was necessary to consider the importance of this factor, if any, in determining the response to anterior pituitary extract.

Very many observations on the influence of infection on glucose tolerance have been published but reference will be made only to a few of the more recent investigations. It has been shown (Williams and Dick, 1932) that 41 per cent. of patients with acute infections will develop glycosuria if given a sufficient quantity of sugar and that similar findings are obtained in the case of experimental animals. In human subjects this diminution in sugar tolerance was observed to persist for a period of some weeks to some months after the infection has cleared up. Since the glycosuria in these cases disappeared when insulin was given it was concluded by these authors that the toxaemia of an acute infection interfered with the action or production of insulin by the pancreas. MacBryde (1933) confirmed the fact of these observations and observed that during an infection the hypoglycaemic action of insulin was diminished and that a state of relative resistance to insulin developed. Schmidt and his

co-workers/

co-workers (1934) stated as a result of their studies that any infection, pyogenic or non-pyogenic, febrile or afebrile, of the skin or of the joints, resulted in a definite disturbance of carbohydrate metabolism, or at least in the rate at which sugar disappeared from the blood, but did not commit themselves to any statement of opinion as to the mechanism by which the diminution in carbohydrate tolerance was produced. Similar findings have been obtained by many groups of workers and it would serve no purpose to refer to any more. Agreement is general concerning the fact that tolerance is lessened during infection but the actual cause for this disturbance of metabolism is not certain. Sweeney (1928) assumed that infection interfered with the production of insulin in the pancreas; Lawrence (1927) was of the opinion that fever produced its effect by stimulating the thyroid and adrenal glands; Karelitz, Cohen and Leader (1930) considered that under conditions of infection insulin was destroyed or inactivated by the products of the infection; Corkill (1932) was impressed by the complicated nature of the problem and concluded that toxins interrupted the complex chain of events leading to the storage of glycogen in the liver, when an injection of insulin or adrenalin is made in the young rabbit. Fortunately for present purposes it is unnecessary to decide what is the most likely manner in which infection disturbs glucose tolerance, all that is required is an understanding that such actually happens.

Method. The subjects chosen were patients under the care

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of Mr. J. Scouler Buchanan in the Western Infirmary who were suffering from some septic infection. After a preliminary blood sugar curve had been carried out anterior pituitary extract was given in quantities of one c.cm. daily for a period of 3 days, and the glucose tolerance again estimated.

Assessment of Results. It was evident that any change which might be noted in the glucose tolerance was not necessarily due to the action of the anterior pituitary extract alone: it was possible that any alteration that occurred might be due to some change in the septic infection from which the individual was suffering. At first an attempt was made to classify the results according as to whether the infection had become more or less severe in the interval between the 2 blood sugar curves, but it soon became evident that any change noticed might be largely a matter of personal opinion. There was a tendency to regard any increase in sugar tolerance being due to a lessening of the severity of the infection, rather than to any effect of the extract, and this was soon followed by a tendency to regard any increase in sugar tolerance as evidence that some improvement in the condition had actually occurred, although other signs that this happened might be scanty. In some cases there could be no doubt that a change had taken place in the severity of the infection, but in the majority of instances it was most difficult to make any decision on this point without being influenced by the blood sugar findings. It was therefore decided to regard the subjects

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as a group and to compare the average findings obtained before any extract was given with those obtained afterwards, and not to place any stress on the results obtained in individual cases.

Results. A total number of 10 cases were examined in the manner described: in 8 instances the effect of the extract was to cause a decrease in glucose tolerance, and in the remaining 2 cases an increase was observed. When the results are viewed as a whole it will be seen that the usual action of the extract was to produce a decrease in glucose tolerance. These results are summarized in Table 17 and Fig. 18.

Discussion. The results show that, in the presence of an obvious infection, the usual effect of injection of anterior pituitary extract is to cause a decrease in carbohydrate tolerance. Exceptions to this rule did occur but they were in the minority, and in general the results obtained with this group of subjects present a striking contrast to those secured in a number of individuals in good health. Since it is unlikely that the diet of the infected subjects varied greatly in its carbohydrate content from one case to another, it may be concluded that the presence of infection is a factor of importance in determining the nature of the response to anterior pituitary extract.

Two factors have now been recognised that are of importance in influencing the response of the individual to extract of the anterior/

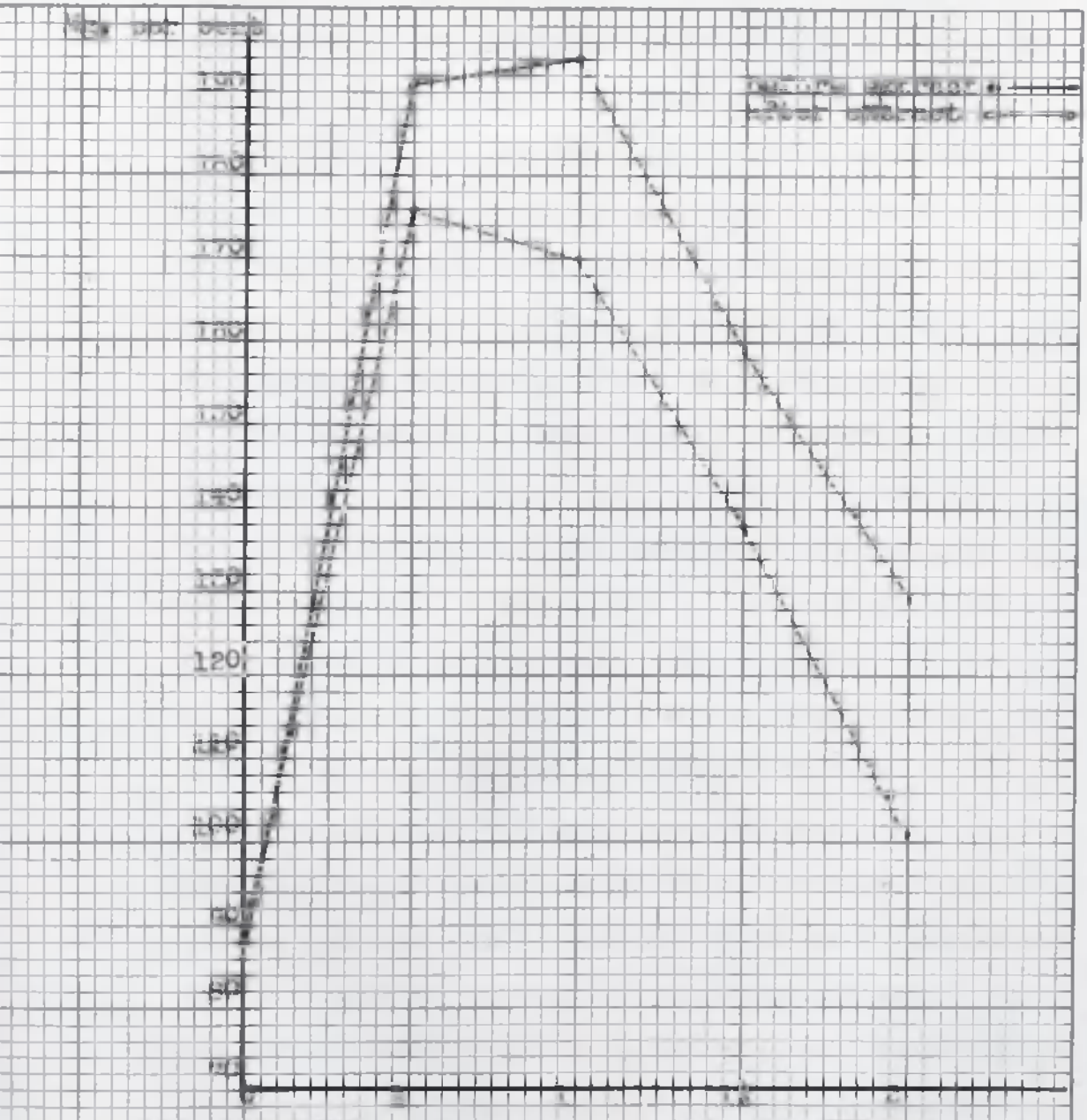

Fig. 10 Effect of anterior pituitary extract in the presence of an infection.

anterior lobe of the pituitary, the factor of infection and that of the carbohydrate intake. It is of some interest to discuss which of these is the more important so far as the present investigation is concerned. In discussing the importance of the carbohydrate intake in this connection it was observed that there was a close relationship between the composition of the diet and the response to the extract, but it was also pointed out that this relationship was not absolute since exceptions occurred and because of this other factors must be sought. Before any reference is made to one of the other factors that might be operative, that of infection, it is interesting to examine the evidence on which the importance of the carbohydrate of the diet in this connection is based. In order to demonstrate the influence of the quantity of carbohydrate 2 different diets were given, one containing 50 grams of carbohydrate and the other 500 grams. When this was done it was possible to demonstrate the importance of this factor in deciding the response to the extract. However no proof was advanced that smaller differences in the carbohydrate intake would have had a similar effect and no opinion can be expressed on this point. This position is unsatisfactory, because it is certain that the daily intake of carbohydrate, in the case of the patients taking ordinary diet and given pituitary extract, would not show a difference of this magnitude from one individual to another. Minor differences would certainly exist but there is no evidence that these would have given rise to such

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a clear cut difference in the response to the extract, such as was observed when the special diets were given. The conclusion is reached that, while there is no doubt that the response to pituitary extract can be altered by changing the carbohydrate ration, it is doubtful if differences in the carbohydrate intake can explain the variation in response seen in a group of normal subjects taking ordinary diet. Under these circumstances another likely factor must be sought in explanation and this may well be the presence or absence of an infective process, which might be latent and not readily recognised by clinical methods. Other factors almost certainly exist, but no evidence as to their nature has been discovered in the course of the investigation and so this problem cannot be pursued further at the present time.

Throughout this investigation attention has been paid to the possibility of producing a temporary diabetic state by means of injection of anterior pituitary extract. In those who exhibited a diminished sugar tolerance as the result of these injections the effect of continuing the injections was tried, with the result that the hyperglycaemia was shown to be of a temporary nature. The combination of the high carbohydrate diet and anterior pituitary extract was also shown to have only a temporary effect. Comment has already been made concerning the influence of an infection in producing hyperglycaemia and glycosuria and since there is a close relationship between these 2 conditions, it is not surporising that infection as a factor of importance in the

aetiology/

aetiology of diabetes mellitus has excited the attention of many. In the opinion of Joslin (1935) infections are not considered to be of great aetiological importance in diabetes mellitus since, in childhood cases where one would expect the highest correlation, 90 out of 100 children had no infection within a year of the onset. On the other hand John (1934) found that 20 per cent. of his chuldhood cases had an infection within 2 months of the onset, and Barach (1927) also found a high incidence of infection. However, even if one allows that there is a fairly high incidence of infection prior to the onset of diabetes mellitus, that is not to say that infection is of the greatest importance as a causal factor. If this were so then not only would there commonly be a history of infection in cases of diabetes mellitus, but there would be a high incidence of diabetes mellitus in cases of infection, and this is not so. Nevertheless it is evident that in a small proportion of cases the onset of diabetes mellitus is preceded by an infection and, since it has been shown that when infection is present anterior pituitary extract causes a decrease in carbohydrate tolerance, the possibility that these cases might be due to a combination of infection and pituitary overactivity at one and the same time had to be considered. It was therefore necessary to determine whether the administration of a larger quantity of anterior pituitary extract than that previously used during the course of a septic infection might lead to the production of a temporary diabetic state.

Method./

Method. The subjects chosen for study were similar to those in the previous experiment and were all suffering from septic infections. After a preliminary glucose tolerance test anterior pituitary extract was given in quantities of one c.cm. daily for 7 days. At the end of this period the glucose tolerance was again estimated.

Results. As in the previous experiment the results were classified according to the alteration observed in the peak values of the blood sugar curves, but the individuals were regarded as a group and no stress was placed on the results obtained in single cases. A total number of 13 cases were studied in this way: in 8 instances a loss of sugar tolerance was noted following the injection of anterior pituitary extract, and in 5 instances a gain in tolerance was noted. These results are summarized in Table 18 and Fig. 19.

Discussion. When these results are compared with those obtained in a similar group of subjects given a smaller amount of extract there is nothing to suggest that a diabetic state might be produced in this way. Throughout the whole investigation a similar result has been apparent. Attempts have been made to produce a temporary diabetic state in several ways: by continuing the injection of extract when an initial decrease in tolerance had been noticed; by giving pituitary extracts at the same time as a high carbohydrate diet; by injecting anterior pituitary extract

during/

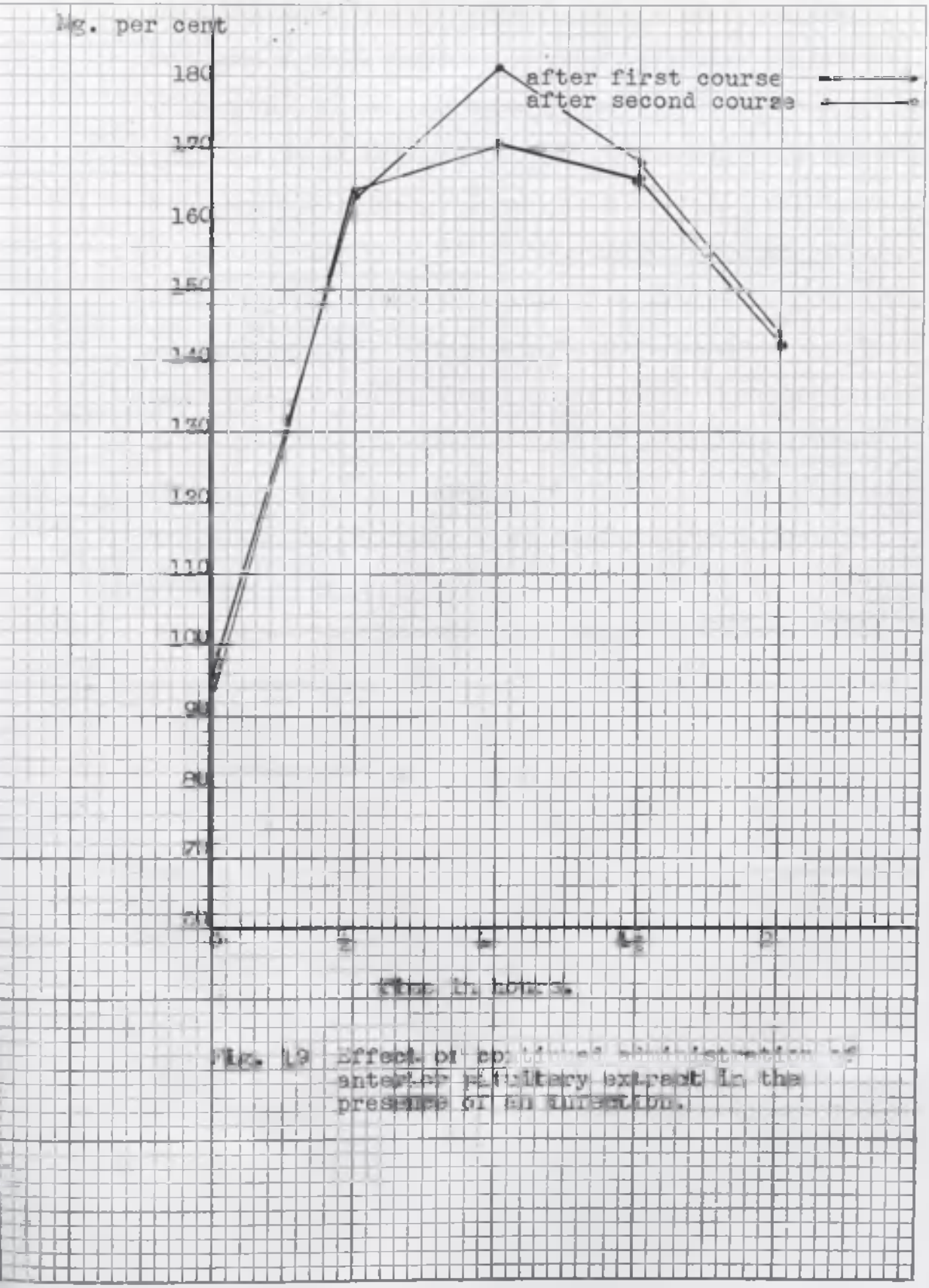

Fig. 19 Effect of co[illegible] antelopic pituitary extract in the presence of an anesthetic.

during the course of an infection. In no instance has there been any convincing evidence that more than a temporary failure could be produced by these means, and the conclusion may be drawn that a healthy pancreas can compensate for any of the loads put on it during this study. In connection with this last statement it should be remembered that the presence of sufficient pancreatic tissue has been found to be capable of masking the diabetogenic action of anterior pituitary extracts in laboratory animals (Russell, 1938). This finding accords well with the results obtained in human subjects throughout the present investigation. In the same way it is reasonable to conclude that in the presence of a pancreatic insufficiency the diabetogenic action would be more intense, indeed this has been shown to be so in the partially depancreatized experimental animal (Houssay and Biasotti, 1931b; Bennett and others, 1938).

Table 17.

The Effect of Injection of Anterior Pituitary Extract on Carbohydrate Tolerance in the Presence of an Infection.

Case.	Age.	Sex.	Disease.	Amount.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
129.	27 yr.	M.	Septic hand.	0	96	161	175	126	116	
				3 c.cm.	92	140	192	176	173	+17
130.	27 yr.	M.	Sacral Tuberculosis.	0	77	147	182	127	120	
				3 c.cm.	88	196	200	142	103	+18
131.	47 yr.	M.	Osteomyelitis.	0	81	189	175	125	81	
				3 c.cm.	81	204	217	202	149	+28
132.	22 yr.	M.	Empyema.	0	75	178	153	122	76	
				3 c.cm.	180	169	149	145	119	-9
133.	20 yr.	M.	Osteomyelitis.	0	105	169	192	217	145	
				3 c.cm.	94	175	196	222	179	+5
134.	25 yr.	M.	Osteomyelitis.	0	90	156	112	98	78	
				3 c.cm.	86	181	153	128	105	+25
135.	29 yr.	M.	Osteomyelitis.	0	88	192	188	133	59	
				3 c.cm.	91	182	185	127	98	-7
136.	44 yr.	M.	Cellulitis.	0	97	200	196	205	161	
				3 c.cm.	86	228	238	164	105	+38
137.	57 yr.	M.	Osteomyelitis.	0	90	167	175	128	95	
				3 c.cm.	94	192	178	166	161	+17

Table 17. (Contd.)

Case.	Age.	Sex.	Disease.	Amount.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
138.	27 yr.	M.	Septic hand.	0	92	205	151	97	79	
				3 c.cm.	92	244	233	122	95	+39
Mean:					89	176	170	138	101	
					88	191	194	159	129	

Table 18.

The Effect of Continued Injection of Anterior Pituitary Extract on Carbohydrate Tolerance in the Presence of an Infection.

Case.	Age.	Sex.	Disease.	Amount.	Blood Sugar mg /100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
139.	36 yr.	F.	Puerperal Mastitis.	0	88	128	222	204	196	
				7 c.cm.	97	166	187	233	182	+11
140.	30 yr.	F.	Puerperal Mastitis.	0	90	133	159	126	107	
				7 c.cm.	94	164	189	145	161	+30
141.	43 yr.	F.	Pelvic Cellulitis.	0	75	227	204	181	154	
				7 c.cm.	74	145	197	151	126	-30
142.	39 yr.	F.	Septic Hand.	0	102	149	181	214	172	
				7 c.cm.	88	135	169	149	69	-45
143.	42 yr.	F.	Burn.	0	111	176	209	192	172	
				7 c.cm.	105	156	227	222	197	+18
144.	35 yr.	M.	Osteomyelitis.	0	119	156	181	156	141	
				7 c.cm.	110	164	199	143	151	+18
145.	45 yr.	M.	Empyema.	0	106	147	133	176	123	
				7 c.cm.	88	124	99	89	88	-52
146.	35 yr.	F.	Puerperal Mastitis.	0	102	161	176	145	120	
				7 c.cm.	106	204	197	143	130	+28
147.	58 yr.	F.	Septic Arthritis.	0	88	119	118	109	110	
				7 c.cm.	98	127	170	180	149	+61

Table 18. (Contd.)

Case.	Age.	Sex.	Disease.	Amount.	Blood Sugar mg./100 c.cm. 0 hr.	½ hr.	1 hr.	1½ hrs.	2 hrs.	Rise or Fall in mg./100 c.cm.
148.	12 yr.	M.	Osteomyelitis.	0	94	189	239	146	122	
				7 c.cm.	106	259	181	212	192	+20
149.	45 yr.	M.	Osteomyelitis.	0	96	164	174	156	113	
				7 c.cm.	87	143	227	181	172	+53
150.	25 yr.	F.	Puerperal Mastitis.	0	88	194	218	176	164	
				7 c.cm.	93	170	179	161	132	-39
151.	15 yr.	F.	Septic Adenitis.	0	86	176	239	204	175	
				7 c.cm.	81	181	193	143	110	-46
Mean:					96	163	181	168	144	
					94	164	171	166	143	

Section Twelve.

On the Relationship between the Anterior Lobe of the Pituitary and Clinical Diabetes Mellitus.

As has been pointed out, the connection that exists between the clinical conditions of hyperpituitarism and the production of glycosuria and diabetes mellitus has always excited enquiry as to the possibility of a pituitary factor in the causation of diabetes mellitus. This interest has not been diminished as the result of the observations on the influence of the hypophysis in experimental diabetes. The alleviation of pancreatic diabetes in experimental animals following hypophysectomy, and the demonstration of a diabetogenic property in extracts of the anterior lobe of the pituitary served to emphasize the possibility that a close relationship existed between the hypophysis and the pancreas. However so far as clinical diabetes is concerned the connection is not so obvious: there can be little doubt that in certain cases, for example acromegalics, the diabetes is due to the presence of an anterior pituitary factor, but the great majority of cases of diabetes mellitus present no clinical evidence of any overactivity of the hypophysis. It may be that this failure to recognise any overactivity of the anterior pituitary lobe in the majority of cases of diabetes mellitus is due to the absence of any method of measuring the activity of this gland; in this way recognition of hyperpituitarism cannot be made until obvious clinical signs develop,/

develop, such as disturbance of growth. However it is not improbable that minor degrees of oversecretion and temporary overactivity may pass unnoticed. In this connection in the work of Young (1937, 1938) in producing permanent diabetes in dogs by means of the injection of anterior pituitary extract is of great interest. As has been mentioned, this work represents the first convincing demonstration that permanent diabetes could be produced in experimental animals by the injection of an extract of the pituitary, and an important feature of the experiment was that the diabetes persisted after the extract had been stopped. Young (1939) makes the interesting comment that, if the results obtained in producing experimental diabetes in animals are of significance in human diabetes mellitus, it is possible that a short period of pituitary overactivity in a human subject might result in damage to the islets of Langerhans so as to produce a diabetic state, although no persistent sign of pituitary overaction might be found. In such a case the diabetes might appear to result primarily from islet lesions. This suggestion may prove to be of importance but it is impossible of proof in the absence of any means of assessing pituitary activity other than by the presence of gross clinical signs. It is however possible to examine some of the factors which are believed to be of importance in deciding the onset of diabetes mellitus in the light of this suggestion.

Until now no comment has been made concerning either the composition or the identity of the factor present in crude anterior pituitary extracts and playing an important part in the metabolism

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of carbohydrate. No useful purpose would be served by considering the views of various workers concerning the composition of this substance, since there is no general agreement on this subject; but there is a suggestion regarding its identity that is of great present interest and must therefore be mentioned. Young (1939), in reviewing the relation of the anterior pituitary to carbohydrate metabolism, remarks that the growth hormone may be identical with the diabetogenic substance and says that the evidence at present available is compatible with such an idea. If this is so then it is possible to consider the incidence of diabetes mellitus in human subjects at the period of active growth, and in this way consider the possible importance of overaction of the anterior pituitary as a causal factor in the production of the disorder. Attention has already been directed towards this field of study by certain investigators. White (1935, 1936) in particular has made important observations: in a series of 303 diabetic children overheight was noticed amounting to an average of 2.4 inches in 87 per cent of the cases. If this overgrowth is regarded as a sign of temporary overactivity of the pituitary these cases may be compared to the dogs treated intensively with anterior pituitary extract and developing permanent diabetes as the result. Personal experience of one case was striking: a boy, aged 18 years, grew a total of 4 inches between his 17th and 18th birthdays, at the end of this period diabetes developed and required 40 to 50 units of insulin daily to control the glycosuria. Since the normal increase in height at this age is only 0.5 inches there is

some/

some justification for considering this as an example of an over-active anterior lobe of the pituitary. There is therefore some evidence that overactivity of the pituitary may be a factor in the causation of certain cases of diabetes in childhood.

Although it may seem reasonable to suppose that a temporary overactivity of the pituitary may play a part in the production of diabetes in early life, no such close relationship can be demonstrated in connection with the majority of cases - those occurring in adult life. In adult life some measurement of pituitary activity may be obtained by a consideration of the sexual processes and Joslin (1935) points out that the incidence of diabetes is somewhat increased at puberty and at the menopause in females; but pregnancy has not been found to cause an increased incidence. The influence of puberty and the menopause in this connection may be due to the increase in pituitary activity at these times, but even if this is so only a small number of cases can be explained on this basis. On the other hand, 80 out of 100 adult cases of diabetes mellitus have a history of previous obesity and this relationship is too close to be merely a matter of coincidence (Joslin, 1935). Obesity is therefore the most important single cause of diabetes mellitus, and so far as the present writer is aware no worker has ever blamed obesity on <u>overaction</u> of the pituitary, indeed the tendency is to regard many examples of obesity as the result of hypopituitarism. Of course all these arguments are based on indirect evidence concerning the activity of the pituitary in clinical diabetes mellitus; direct evidence on this point is scanty. De Wesselow and Griffiths (1936)/

(1936) were able to demonstrate that the plasma of certain elderly diabetics, when injected into rabbits, was capable of checking the development of insulin hypoglycaemia in these animals. The interest so far as this observation was concerned rested in the resemblance between this action of diabetic plasma and extracts of the anterior lobe of the pituitary. Further work may demonstrate the existence of a pituitary factor in the majority of cases, but until this is done there seems little reason at present to blame the pituitary as a causal factor of paramount importance in clinical diabetes mellitus.

Pathology is also of little assistance in deciding the importance of the pituitary gland in this respect, except in providing negative evidence: Eisenhardt (1938) examined serial and random sections of the pituitary in a series of cases of diabetes mellitus. The cases were chosen so as to give a fair cross section of the diabetic population but no constant significant change in the pituitary was found. This conclusion is in agreement with that reached by Warren (1938).

Houssay (1936a) attempted to explain the incidence of diabetes mellitus in terms of the degree of activity of the pituitary, and suggested that the pituitary exerted its influence in 2 ways, hyperactivity and hypoactivity. Hyperactivity was observed clinically by the occurrence of overgrowth in diabetic children, and also by the increased incidence of the disease at puberty and the menopause, and was theoretically associated with an excess of

the diabetogenic factor of Houssay. In contrast to this obesity in the adult, and dwarfism in the child suggested hypoactivity of the pituitary, and could be associated in theory with a lack of the pancreotropic hormone of Anselmino and Hoffmann. This explanation may be regarded as an ingenious attempt to apply experimental findings to a clinical problem, but it is not difficult to find obstacles that stand in the way of its acceptance. Such an explanation does not take into account the fact that injection of the diabetogenic substance in the usual quantities into normal animals produces only a temporary glycosuria, and not a permanent diabetes. It is true that the work of Young has altered this, at least for very large quantities, but this was not known at the time of Houssay's suggestion. Again, to explain the existence of diabetes in cases of dwarfism as being due to the absence of a pancreotropic hormone secreted by the pituitary is at first sight attractive, but, as has been mentioned previously, there is no convincing evidence that any such substance exists. Therefore, for the present writer at least, this hypothesis will not bear critical analysis.

As the result of the intense interest which has been shown in recent years concerning the diabetogenic activities of the anterior pituitary, comparatively little attention has been paid to the response which the pancreas normally makes to this stimulus, but it will be agreed that the existence of a pancreatic defect might lead to the production of diabetes in the presence of a <u>normal</u> output of diabetogenic substance from the anterior pituitary.

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Such cases might also be regarded as being due in part to a pituitary factor. Reference has already been made to the experimental work dealing with the enhanced diabetogenic effect of pituitary extracts in the partially depancreatized animal, and these have been of some interest in the present investigation as demonstrating a means of abolishing the normal compensatory response. This suggestion, that the influence of the pituitary as a common cause in clinical diabetes is most likely to be effective when a pancreatic deficiency is present, has not been found in the literature reviewed during the present investigation and is of great interest to the writer since it agrees well with the results obtained when anterior pituitary extract was given to human subjects under the various conditions which have been mentioned. The hypothesis that the pituitary does not play the primary part in the production of diabetes mellitus, but is only of importance when the pancreas is unable to make a satisfactory response, is in agreement with the conclusions reached by Himsworth (1939) in his extensive review of the mechanism of diabetes mellitus. This worker concluded that, although there is evidence that the pituitary gland may be responsible for the diabetes associated with hyperpituitarism, there is as yet no proof that this gland plays a primary part in the mechanism of other cases of diabetes.

Should this hypothesis prove acceptable another point of interest emerges. Allen (1922a, 1922b) as the result of his classical researches on which the under-nutrition treatment of diabetes was based, showed that in dogs from which sufficient

pancreatic/

pancreatic tissue had been removed to render them on the verge of diabetes, overfeeding precipitated diabetes, whereas with underfeeding diabetes did not develop. The islets of Langerhans in the pancreas of the dogs made diabetic by overfeeding showed typical degeneration, apparently similar to that produced in normal dogs by the injection of anterior pituitary extract (Richardson and Young, 1938). It would be indeed interesting if the only satisfactory hypothesis concerning the production of diabetes existing 20 years ago, that of overfeeding in the presence of a pancreatic deficiency, could be brought into line with modern views on the importance of a pituitary factor.

If it is accepted that some cases of diabetes mellitus may be due to a failure on the part of the pancreas to respond to the normal secretion of the pituitary, rather than to the presence of an excess of pituitary secretion, it will be recognised that no direct proof of the existence of any such pre-diabetic pancreatic deficiency has been advanced, but, for that matter, no excess of pituitary secretion has ever been convincingly demonstrated either. A somewhat similar position has developed with regard to the causation of of exophthalmic goitre. Ever since the discovery that the thyrotropic hormone of the anterior pituitary is capable of producing the features of exophthalmic goitre when injected in experimental animals a search has been made for the existence of an excess of this substance in human subjects of the disease. As in the case of diabetes mellitus, these researches have been largely in vain, and this has induced Marine (1935) and Loeser (1937)/

(1937) to suggest that the development of hyperthyroidism in these cases may be due to a breakdown in the processes which normally protect the gland against the influence of the thyrotropic hormone, rather than to an excess of the hormone itself. It is not impossible that a similar condition may exist in clinical diabetes mellitus.

So much for the possible influence of the pituitary as a factor in diabetes mellitus, but throughout this investigation emphasis has been laid on the finding that the pancreas can apparently compensate for an oversecretion of the pituitary, and it is interesting to review the glucose tolerance at those periods of life when the pituitary is active. Reference has already been made to the frequent occurrence of overheight in diabetic children and to the possible effect of hyperpituitarism as the causal factor in these cases. It has been agreed that this may be the explanation in certain cases, but it cannot be a potent cause of diabetes since, if it were so, then diabetes might be expected to be most common at the period of life when growth is most active, but this is not the case. Joslin (1935) in an analysis of 6537 cases of diabetes showed that the onset of the disease was before the 15th birthday in only 528, and before the 5th birthday in only 117 cases. Therefore since diabetes mellitus is relatively uncommon during childhood it is unlikely that overactivity of the pituitary can be an important primary cause of the disorder; but is there any evidence that diminished glucose tolerance is common at this period of life, as might be expected when the state of activity of the pituitary is considered?

Badenoch and Morris (1936) in an examination of the course of the blood sugar curve in healthy children found that older children showed a definitely higher rise than the younger. The adult type of curve was seldom found before the age of 4 years, was gradually approached in the next 4 years, and became the rule rather than the exception after 8 years of age. Therefore the younger the child the greater the chance of a low blood sugar curve, but during the first year of life the approximate normal growth is 9 inches; during the second it falls to 4 inches; during the third 3½ inches, and in the fourth 3 inches. Thereafter the approximate annual increase in height during childhood is 2 inches. That is to say that the more active the growth of the individual the lower the blood sugar curve. If the growth hormone is identical with the diabetogenic substance as has been suggested the low blood sugar values obtained during infancy and early childhood may well represent the reaction of the pancreas to the stimulus provided by the pituitary.

The action of the anterior lobe of the pituitary at this period of life is not the only factor to be considered when an explanation is sought for the high degree of glucose tolerance found in early childhood; the composition of the diet must also be taken into account as in adult subjects. An infant, aged 6 months and weighing 6.8 kilos., who is given 2 pints cows' milk daily takes approximately 9 gm. carbohydrate per kilo. body weight; and an adult weighing 68 kilos. and taking 400 gm. carbohydrate takes only about 6 gm. per kilo. The effect of the low carbohydrate diet on the glucose tolerance of infants has not been studied/

studied with the same frequency as in the case of adult subjects but the glucose tolerance of the undernourished infant has often been examined. Brown (1925) found that the blood sugar curve in these circumstances after the ingestion of glucose was similar to that of healthy infants. However Badenoch and Morris found that the blood sugar curve in undernourished infants was lower than normal in all cases, and in scrutinizing the results of Brown observed 5 cases of low blood sugar values in her undernourished cases. It may be concluded from these findings that a reduction in the carbohydrate intake of the infant does not reduce glucose tolerance in the same way as it would in adults. In the face of this conclusion it may be maintained that the total quantity of carbohydrate taken in the diet is not the most important factor in determining the high degree of glucose tolerance shown by infants, and in view of the findings of the present investigation the author believes that it may be explained by considering the response to the action of the anterior lobe of the pituitary. This explanation is made the more likely when it is recognised that in the young the impulse to grow is very great; growth in height may take place when there is no gain and sometimes when there is an actual loss of weight (Holt and McIntosh, 1933). Under these circumstances it is not difficult to understand why the undernourished infant maintains a low blood sugar curve when the intake of carbohydrate is diminished.

SUMMARY.

(1) The injection of anterior pituitary extract in human subjects causes an increase in glucose tolerance in the majority of cases. In the minority an initial decrease in glucose tolerance is observed but this disappears when the injections are continued. In those instances where a gain in tolerance results from the injections, the peak value of the blood sugar curve before the extract is given is usually more than 150 mg.; in the cases showing a decrease in glucose tolerance after the injections the peak value is usually less than 150 mg.

(2) When posterior pituitary extract is administered in the same way as anterior pituitary extract the results are similar, both as regards the effects on glucose tolerance and the difference in the peak values of the 2 groups.

(3) The injection of adrenalin hydrochloride under the same conditions leads to an increase in glucose tolerance in the great majority of cases, any loss of tolerance produced in this way being rare.

(4) When extracts of the anterior and posterior lobes of the pituitary are given to human subjects it is possible to alter the response of the subjects by changing the daily intake of carbohydrate. When a high carbohydrate diet is being taken the injection/

injection of pituitary extract usually causes a decrease in glucose tolerance, while when a low carbohydrate diet is being taken the usual effect of the extract is to cause a gain in sugar tolerance. The relationship between the carbohydrate intake and the nature of the response to pituitary extract is close, but is not absolute since exceptions to the general rule occur.

(5) If the injections of pituitary extract are continued while the individual is taking a high carbohydrate diet the ultimate effect is that tolerance is regained, and a progressive loss of tolerance to glucose cannot be secured in this way.

(6) When certain individuals are suddenly changed from a low to high carbohydrate diet there is a temporary loss of glucose tolerance, and it is necessary to wait for a period of from 14 to 17 days before normal tolerance is regained.

(7) When a group of individuals are subjected to the same conditions of low carbohydrate intake the loss of glucose tolerance varies considerably from one case to another.

(8) The injection of adrenalin over a period of some days is capable of preventing to some extent the loss of tolerance to glucose which normally occurs when a low carbohydrate diet is being taken.

(9) In the presence of an infection the injection of anterior pituitary extract usually results in a decrease in glucose tolerance. When the injections are continued there is no evidence that a progressive diminution in glucose tolerance can be produced in this way.

Conclusions.

(1) The administration of anterior and posterior pituitary extracts to human subjects causes a temporary diminution in glucose tolerance in certain cases, but if the extracts are continued the ultimate effect is an increase in tolerance. Since this property of increasing glucose tolerance is shared by extracts of both lobes of the pituitary gland, it cannot be due to the presence of a specific substance stimulating the production of insulin, but must be largely the result of the hyperglycaemia following the injection of the extracts.

(2) The injection of adrenalin results in an increase in sugar tolerance in the vast majority of cases, any loss of tolerance due to this procedure being rare. Since adrenalin causes a hyperglycaemia without inducing a condition of insulin resistance, in contradistinction to pituitary extracts, the temporary loss of tolerance seen when pituitary extract is injected is probably the result of the neutralization of the insulin secreted. The action of pituitary extract cannot therefore be explained by considering its property of causing a hyperglycaemia, without taking into account the production of insulin resistance.

(3) The nature of the response to pituitary extracts is influenced by the carbohydrate intake. When a large amount of carbohydrate/

carbohydrate is being taken the pancreas is temporarily unable to cope with the added burden of the pituitary extract and a loss of sugar tolerance results. When a small amount of carbohydrate is being taken the pancreas is able to respond rapidly to the action of pituitary extracts and loss of tolerance seldom occurs. This may in part provide the explanation for the existence of the two types of response.

(4) Even when a high carbohydrate diet is being taken continued administration of pituitary extracts results ultimately in an increase in glucose tolerance, illustrating the ability of the healthy pancreas to cope with any load put on it.

(5) When a low carbohydrate diet is being taken there is l little stimulation of insulin production. On increasing the intake of carbohydrate in certain cases the pancreas is temporarily unable to produce sufficient insulin and hyperglycaemia results.

(6) In some cases the adoption of a low carbohydrate diet causes comparatively little decrease in glucose tolerance as compared with others. Since the control of insulin production is largely a matter of the quantity of carbohydrate in the blood, an increased production of sugar from an endogenous source might account for the high degree of glucose tolerance in these cases. The action of adrenalin in compensating for an absence of the normal post-prandial hyperglycaemia so far as the maintenance of normal glucose tolerance is concerned, lends support to the view that in these individuals there may be an excess of hyperglycaemic substances secreted from one or other of the endocrine glands at the time of the experiment, the hyperglycaemia produced in this way accounting for the high glucose tolerance seen when the

dietary/

dietary carbohydrate was low.

(7) The endocrine control of the blood sugar level is a matter of the action of certain glands and the response made by their antagonists. To explain a low blood sugar curve simply on the grounds that a contra-insular substance is lacking does not provide an accurate explanation for all such cases. The low blood sugar curve may be the result of an effective response on the part of the pancreas to the presence of a hyperglycaemic substance. Conversely a high blood sugar curve may not mean that an excess of a contra-insular hormone is present; it may be the result of defective production of insulin in the absence of any endocrine stimulus for its production. The carbohydrate intake must also be considered in interpreting blood sugar curves in terms of glandular activity. A large intake of carbohydrate enhances the hyperglycaemic action of certain extracts, and a low carbohydrate may conceal the presence of hyperglycaemic substances in excess of normal. It is also probable that a high carbohydrate diet may mask the absence of contra-insular hormones by providing an alternative stimulus for insulin production.

(8) In the presence of an infection the usual effect of anterior pituitary extract is to cause a decrease in glucose tolerance, but no evidence was obtained that might lead to the conclusion that diabetes mellitus might be, in some cases, the result of an infection with a co-existing pituitary overactivity. It has already been shown that the carbohydrate intake is a factor of importance in determining the response to pituitary extracts; but in order to demonstrate this it was necessary to change the

carbohydrate/

carbohydrate ration in the diet from 50 gm. daily to 500 gm. daily. Since it is very doubtful if the carbohydrate intake of the subjects taking ordinary diet and given pituitary extract varied in such a degree, it is concluded that the presence or absence of a latent infection is probably a factor of greater importance than the carbohydrate intake, in determining the nature of the response of these individuals to pituitary extracts.

(9) There is little evidence that a pituitary factor is of primary importance in the causation of clinical diabetes mellitus, except in acromegaly and possibly some other conditions. The frequent occurrence of overheight in diabetic children might be taken as showing the influence of the pituitary in this connection, but diabetes is less common in childhood than in adult life, whereas the reverse might be expected if pituitary activity was the predominant factor in determining the onset of the disease. Moreover, obesity is the most frequent precursor of diabetes and this is not usually attributed to overactivity of the pituitary. If the diabetogenic substance secreted by the pituitary plays any part in the causation of diabetes mellitus, and it is difficult to deny that this is most likely, in view of the close resemblance between the condition produced in experimental animals and that seen in subjects suffering from the disease, it is in the author's opinion most likely to do so in the presence of a pancreatic defect. Under these circumstances a normal output of the diabetogenic substance could lead to diabetes mellitus, and there would/

would be no necessity to seek the presence of overactivity of the pituitary in order to explain the disease. This hypothesis seems attractive at the present time, especially since it accords with that adopted in explaining the occurrence of clinical hyperthyroidism, another disease which can be produced in animals by means of pituitary substance and in which an excess of pituitary secretion cannot be demonstrated in the human subject. It is admitted that this hypothetical pancreatic defect has not been proved to exist, but since the existence of pituitary overactivity has not been demonstrated either it is felt that aetiological problem has not been further confused and may have been clarified in a small degree.

(10) The low blood sugar curves found in early childhood may be related to the period of most active growth when it is to be expected that large quantities of the growth hormone are being produced. If this hormone is identical with the diabetogenic substance the low blood sugar values may represent the response made by the pancreas to the stimulus.

(11) The conclusions reached regarding the similarity of action of the various endocrine extract used in this study are only valid when the problem is studied in the manner described. There is no suggestion that identical results would have been achieved if different methods had been adopted, or if different quantities of extract had been injected. It is not concluded that anterior and posterior pituitary extracts have the same influence on carbohydrate metabolism, as might be expected from the results obtained, and no opinion is expressed regarding the importance/

importance of the posterior lobe of the pituitary, if any, in this field.

(12) It is evident that the subjects studied could not be regarded as normal subjects, and it cannot be concluded that similar results would have been obtained had a study been made of healthy individuals.

(13) It has been clearly demonstrated that the carbohydrate intake and the presence or absence of infection play a part in determining the response of the individual to pituitary extracts, but it is more than likely that there are other factors.

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