Fashions in Doctors.

Finally, just as there are fashions in pathological theories and in treatments, so there are fashions in doctors. I confess, gentlemen, that I have always been puzzled to explain what makes for success in our profession. It certainly does not seem to be a question of knowledge, nor yet of manners, nor even of character or morals. But if it is difficult to account for ordinary success, it is still more difficult to explain what makes a doctor the "fashion" in his town or district—what makes him, to use an expressive Americanism—"it." We meet the same problem, of course, in other spheres. Why, for instance, of a thousand novels all alike jejune, does one become a "best seller"? Or why does such a song as (let us say) "Yes, we have no bananas" sweep a continent, when a hundred others with equally foolish words and no less catchy an air drop still-born from the lips of the music-hall comedian? "Sir," said Dr. Johnson, "it is in vain to try to explain the inscrutable."

In some cases, of course, a doctor becomes the fashion by skilful self-advertisement, "by toying," as Sir William Osler said, "with the Delilah of the press," but many a man has become the fashion *malgré lui*, and it would be a profound mistake to suppose that all fashionable practitioners are charlatans. On the contrary, many of them have been and are men of whom any profession might be proud; it will suffice, perhaps, to mention Asclepiades in Roman times and Tronchin in eighteenth century France, without referring to more modern examples. Still, one should not envy the fashionable doctor; rather should one wonder at him. He leads a life of slavery, even although, as a wag said, it is slavery on the guinea coast; and, circumstanced as he is, good and thorough work becomes impossible. His position, too, on a pinnacle is always precarious. He has, it is true, his little day, but he is apt to wake up one morning to find that his worshippers have stampeded *en masse* overnight to some newer shrine of the fickle goddess Fashion.

THE EFFECT OF PITUITRIN AND INSULIN ON BLOOD SUGAR:

THEIR ANTAGONISM AND THE MODE OF ITS ACTION.*

BY

R. D. LAWRENCE, M.A., M.D.,
CHEMICAL PATHOLOGIST, KING'S COLLEGE HOSPITAL;
AND

R. F. L. HEWLETT, M.R.C.S., L.R.C.P.,
ASSISTANT CHEMICAL PATHOLOGIST.

RECENT work by Burn¹ on rabbits has clearly shown the antagonism of infundibular extracts to insulin. If given in sufficiently large doses the administration of posterior lobe extracts prevented the fall of blood sugar caused by insulin. He states that this effect is not produced by extracts of the anterior lobe or of any other tissue (except adrenaline). Nor did he find that pituitrin given alone produced such a rise in blood sugar as to account for its almost complete inhibition of insulin action. Some of the doses he used on rabbits were so large, corresponding to about 150 c.cm. for an average human adult, that it was felt that their effect might be partly toxic and at any rate did not permit of the same conclusions being drawn regarding the effect of therapeutic doses in man. Again, these results were obtained in normal rabbits and would not necessarily apply to diabetics. Accordingly the scope of this investigation has been to examine the effect of therapeutic doses of infundibular extract on the blood sugar content of normal and diabetic man, particularly as regards an insulin antagonism. Other points of interest have arisen, especially regarding the site of this antagonism, and are also included in this paper. Parke Davis 10 per cent. infundibular extract (pituitrin) has been used, and care has been taken to use the same batch of insulin. The blood sugar was estimated in duplicate by Maclean's method on blood drawn from the ear, and the

normal persons were all students and residents at King's College Hospital, to whom our thanks are due for some rather trying experiments. Unfortunately we were not able to follow the blood sugar for as long as we wished, but this has not vitiated the results.

Effect of Pituitrin on Blood Sugars in Normal and Diabetic Persons.

The literature is full of contradictions regarding the effect of pituitrin on blood sugar: Borchardt, Cushing, and others state that it causes a rise in blood sugar, and Franchini, Stenstrom, and others deny this. Burn found in rabbits with large doses that sometimes there was a slight rise and sometimes a slight fall. We have investigated this by giving 1 c.cm. subcutaneously to normal and diabetic persons (Tables I and II). The normal persons received their pituitrin three to four hours after breakfast when their blood sugars had returned to a fasting level, and the blood sugars were followed every half-hour for two hours. Of the six cases investigated, three showed no appreciable change—

TABLE I.—Effect of Pituitrin on Blood Sugar of Normal Fasting Individuals.

	Fasting Level.	Pituitrin Injected.	Time (Hours) after Pituitrin.			
			1/2.	1.	1½.	2.
Case A ...	94	2 c.cm.	87	86	77	—
Case B ...	125	1 c.cm.	150	141	—	13
Case C ...	98	1 c.cm.	98	95	93	—
Case D ...	90	1 c.cm.	99	100	93	—
Case E ...	96	1 c.cm.	121	—	120	—

less than 10 mg. per cent.; one showed a drop of 17 mg., and two others a rise of about 20 mg. (Details of five of the six cases are given in Table I.) Consequently we can conclude that pituitrin has no appreciable effect on blood sugar, small changes probably being due to variations in the water content of the blood, as Partos and Katz-Klein² have shown. The three diabetics similarly showed no variation in blood sugar (Table II).

TABLE II.—Effect of Pituitrin on Blood Sugar of Fasting Diabetics.

	Fasting Level.	Pituitrin Injected.	Time (Hours) after Pituitrin.			
			1/2.	1.	2.	2½.
Case A ...	96	1 c.cm.	92	96	97	—
Case B ...	143	1.5 c.cm.	148	156	151	155

Antagonism of Pituitrin to Insulin in Normal and Diabetic Persons.

Having determined the separate effect of a given dose of pituitrin and of insulin in various individuals, we next gave them simultaneously in different parts of the arm. The results (Table III) show the almost completely antagonizing

TABLE III.—Antagonism of Pituitrin to Insulin in Normal Persons.

	Before Insulin or Pituitrin.	Insulin or Pituitrin Injected.	Time (Hours) after Injection.			
			1/2.	1.	1½.	2.
Case I ...	100	Ins. 15 units	81	66*	75*	Glucose given 87
"	92	Ins. 15 units, Pit. 0.8 c.cm.	90	93	91	—
Case II ...	101	Ins. 15 units	85	—	72*	—
"	104	Ins. 15 units, Pit. 1 c.cm.	90	—	91	—

* Symptoms of hypoglycaemia.

effect of pituitrin on insulin. The antagonism is most marked in the first hour, for in some of the cases the insulin seemed to gain the upper hand in the second hour and lowered the blood sugar considerably, though never so low as when insulin was given alone.

* This investigation was carried out with the aid of a grant from the Medical Research Council.

The same antagonism was clearly demonstrated in diabetics. Insulin alone was given one day to certain cases on standard conditions of diet, and on the following day 1 c.cm. of pituitrin was injected at the same time as the insulin. The blood sugar was estimated for five hours, and the results are shown in Table IV. The first entry is the

TABLE IV.—*Antagonism of Pituitrin to Insulin in Diabetics.*

	Fasting Level.	Breakfast and Insulin.	Time (Hours) after Insulin given.				
			1.	2.	3.	4.	5.
Case A ...	109	Ins. 18 units	125	118	82	—	68
"	109	Ins. +1 c.cm. Pit.	162	193	158	—	133
Case B ...	222	Ins. 14 units	253	223	201	185	
"	189	Ins. +1 c.cm. Pit.	276	264	241	213	
Case C ...	139	Ins. 10 units	179	149	133	102	
"	130	Ins. +1 c.cm. Pit.	168	196	164	130	
Case D ...	121	Ins. 15 units	114	90	—	56*	
"	89	Ins. +1 c.cm. Pit.	96	103	79*	58	

* Symptoms of hypoglycaemia.

In Case B the difference before and after pituitrin is more marked if the initial levels are regarded.

fasting level; the injections were then given and breakfast followed half an hour later. Three of the cases showed the antagonism very clearly. The fourth (D) was less definite; he also had the lowest blood sugar level and was on the lowest diet. Presumably he had the least carbohydrate or glycogen store in his body, and it is likely that this is why pituitrin antagonized insulin less than in the other cases; for we will produce evidence to prove that pituitrin mobilizes glycogen and thus counteracts the action of insulin.

Tolerance of Normal Persons for Insulin.

Insulin had its usual effect in lowering the blood sugar of all the normal individuals investigated, and it may be interesting to record the effects of different doses. In every case the insulin was administered three hours after breakfast, when the blood was at a normal fasting level, and the fall of blood sugar was watched for two hours unless the onset of hypoglycaemia supervened before that time. Lilly insulin was used throughout the experiments, as it seemed to be more rapid in action than British.* Doses of 10 units lowered the blood sugar slightly from 10 to 15 mg. per cent., but not sufficiently to cause symptoms of hypoglycaemia. Doses of 15 units lowered the blood sugar by from 15 to 35 mg. in different cases, but caused symptoms only once at a blood sugar level of 66 mg. at the end of one and a half hours. Half an hour later this case had recovered spontaneously without the administration of glucose and the blood sugar had risen to 75 mg. Such a recovery is a well known fact, and would indicate that the discharge of glycogen from the liver is not really inhibited by insulin, as has been stated, and that the store of glycogen is not exhausted when hypoglycaemia does occur, but merely that glycogenolysis is not able to keep pace with the rapid disappearance of sugar from the blood caused by large doses of insulin in normal individuals. Doses of 20 units caused symptoms of hypoglycaemia in both the normal cases to which it was given, but one of them recovered spontaneously and showed higher blood sugars at the end of two than of one hour. Other cases had to be given glucose by mouth, and the time required for recovery was from three to ten minutes. It was thus fairly clear that 15 to 20 units is about the limit of tolerance for normal individuals in the fasting condition.

Another point of interest was to determine the tolerance for insulin of a normal individual on a normal diet. A brave volunteer having been obtained, he was given increasing doses of insulin before breakfast on successive days until symptoms appeared. Blood sugar tests were not

carried out, for it had already been determined that symptoms appeared in his case at about 75 mg. per cent. Two doses a day were not given, both on account of the inconvenience of such a procedure and to avoid depleting his glycogen store. It is assumed that the latter is not likely to be much exhausted by one dose a day, whereas two large doses a day might very well deplete it, so that he would tolerate less insulin as the experiment went on. On each day his breakfast consisted of about 60 grams of carbohydrate, 20 to 30 of protein and fat, and the dose of insulin was increased by 10 units every day. A dose of 40 units was tolerated without any effects, but 45 units of A.B. insulin produced quite severe symptoms about three hours after breakfast. Unfortunately the subject had grown careless about insulin, forgotten all about his injection, and was just setting out on a walk unarmed with sugar when symptoms of weakness, dizziness, and faintness came on suddenly. He managed to reach a toffee shop, and without unnecessary explanations ate a quarter of a pound of toffee and was restored in a quarter of an hour. It seems likely that if he had had some carbohydrate two hours after his insulin the symptoms would never have occurred, and that the normal individual could tolerate over 100 units a day, perhaps far more, if supplied frequently with a large amount of carbohydrate to cover it. While insulin is actually balanced by the active absorption of carbohydrate, no hypoglycaemia occurs.

This experiment tells us little or nothing definite about the effect of an injection of insulin on the production of endogenous insulin, but it is probable that the latter was produced as usual under the stimulus of carbohydrate food. For if no, or little, endogenous insulin had been produced, as in diabetes, we imagine that the carbohydrate of his breakfast and of his glycogen store would have been sufficient to balance 45 units of insulin. This individual tolerated 20 units in the fasting condition with the appearance of only slight symptoms which did not require the administration of glucose to effect recovery.

Certain Symptoms due to Pituitrin.

All the normal individuals who received a therapeutic dose of 1 c.cm. of pituitrin developed unusual and alarming symptoms which we have not found described elsewhere.* From ten to thirty minutes after the hypodermic injection they became a ghastly pale grey colour, and some of them became dizzy, faint, and shaky. This appeared to be due to marked vaso-constriction of the cutaneous and probably of the cerebral vessels. The pulse was not quickened nor was the blood pressure raised. This latter point was confirmed in two cases by the sphygmomanometer, but in the others was merely a clinical impression of the pulse. Fortunately their appearance was more terrifying than their feelings, and the pallor and other symptoms usually passed off by the end of an hour. Now, widely as pituitrin is used in obstetrics, etc., it does not seem to have the above effect, and a few cases which we have recently observed closely (and personally) have not shown even pallor. Both normal men and women have shown these symptoms, but they have been absent in the five diabetics tested. Accordingly, it is not likely to be due to some unusual toxic product, such as histamine, of the special batch of pituitrin used. Moreover, one of our cases of diabetes insipidus who is constantly on the drug nearly always notices this effect if he takes more than 0.5 c.cm. This apparent difference in action of pituitrin on normal persons, diabetics, and women in labour offers an interesting field for confirmation and further investigation. We have no explanatory hypothesis to offer.

Blood Sugar Curves in a Case of Diabetes Insipidus.

Before we attempt to discuss the relation of the pituitrin-insulin antagonism to the wider questions of glycogenic function and carbohydrate metabolism in general some other experiments bearing on the subject will be recorded. It is well known that a lowered carbohydrate tolerance is associated with hyperpituitarism (acromegaly) and a raised tolerance with hypopituitarism (Fröhlich's syndrome, etc.). These diseases are commonly supposed to be associated with disturbance of the anterior lobe of the pituitary

* British insulin has recently become quicker in its action.

* Since this was written similar effects have been described by B. Sacks (*Heart*, vol. xi, No. 4, December, 1924.)

gland which affects carbohydrate metabolism. But it is the posterior lobe, or at least extracts from it, that affect insulin action. Also the carbohydrate metabolism is affected in the following case of diabetes insipidus, although the condition is commonly held to be due to deficiency of the posterior lobe alone. Therefore it would appear that the posterior lobe as well as the anterior is concerned with carbohydrate metabolism.

A young man developed intense diuresis at the end of the war as the result of cerebral malaria contracted in East Africa. It is controlled by pituitrin injections. He also shows evidence of involvement of the anterior lobe in having lost his pubic hair and becoming impotent. His blood sugar curves after 50 grams of glucose given fasting are shown in Table V. In one he had

TABLE V.—Effect of Glucose Meal on Case of Diabetes Insipidus with and without Pituitrin.

	Before Glucose Meal.		Time (Hours) after Glucose Meal.		
			1/2.	1.	2.
0.75 c.cm. pituitrin 15 minutes previously.					
Arterial blood	94	Glucose 50 grams	109	130	100
Venous blood	94		102	120	81
Arterio-venous difference ...	0		-7	-10	-19
No pituitrin for 24 hours.					
Arterial blood	116	Glucose 50 grams	94	101	68
Venous blood	91		88	70	64
Arterio-venous difference ...	-25		-6	-31	-4

had no pituitrin for twenty-four hours, and in the other was given 0.75 c.cm. of pituitrin a quarter of an hour before the test. Without pituitrin he shows an abnormally high tolerance for glucose. Indeed, his curve descends from the fasting level instead of rising. With pituitrin, although the tolerance is still high, there is a very definite difference and the curve is an ascending one. This is seen both in the arterial and venous blood sugar, and in the difference between the two, which is greater without pituitrin.

This arterio-venous difference is absent or very slight in diabetes, and we lay considerable stress on it as an indication of the powers of the muscles to store sugar and abstract it from the blood.³ We presume that it is an index of glycogen synthesis in general, and that the glycogenic function of the liver runs parallel with that of the muscles. We look upon these curves as further evidence that pituitrin lowers the assimilation power for carbohydrate, interferes with the glycogenic function, and perhaps actually causes glycogenolysis.

Mode of Action of the Pituitrin-Insulin Antagonism.

The action of insulin on blood sugar and glycogen stores is little enough understood, but the effect of pituitrin is still more obscure. It is known that pituitrin inhibits the glycogenolysis of adrenaline and anaesthetics, and therefore, when it antagonizes insulin, it hardly seemed likely that it does so by stimulating glycogenolysis. To determine the latter point more definitely, we have taken advantage of the well known action of ergotamine in paralysing the sympathetic and preventing glycogenolysis. Ergotamine prevents adrenaline hyperglycaemia and also enhances the action of insulin¹ in lowering blood sugar by inhibiting the mobilization of sugar from the glycogen of the liver. Therefore we have investigated the pituitrin-insulin antagonism on rabbits under the influence of ergotamine tartrate. In the first group of experiments blood was obtained from the ear veins, but this was found so difficult in ergotaminized rabbits that blood was obtained by heart puncture in all the latter experiments. The same rabbit was used for all the experiments.

The results of the first group of experiments is given in Table VI and Fig. 1. In Experiment A, 5 mg. of ergotamine was given intravenously to a normal rabbit who had received no food for eighteen hours. Two hours later 3 units of insulin (Lilly) were given subcutaneously and the blood sugars followed until they had fallen from 112 to

TABLE VI.—Effect of Ergotamine on Pituitrin-Insulin Antagonism in a Rabbit.

(For description see text.)

Time in Minutes.	Experiment A.	Experiment B.	Experiment C.
—	5 mg. ergotamine 1 hr. 40 mins. before zero	No ergotamine	No ergotamine
0	112	138	153
0	3 units insulin	3 units insulin	3 units insulin
25	90	—	109
45	67	—	—
65	58	77	77
—	1 c.cm. pituitrin	1 c.cm. pituitrin	—
85	48*	91	—
95	35	—	69
110	37	83	—
120	32	—	63
135	Glucose given	77	—

* Symptoms of hypoglycaemia.

FIG. 1.—For description see text and Table VI.

58 mg. per cent. at the end of one hour. Then 1 c.cm. of pituitrin was administered and found to have no antagonizing effect on insulin, as the blood sugar steadily dropped during the next hour. Macleod, Banting, and Burn have shown that, without ergotamine, pituitrin always causes a rise of blood sugar at this stage.¹ Symptoms of hypoglycaemia appeared, requiring the administration of glucose, and the animal did not fully recover for another hour.

The same experiment was repeated fourteen days later with identical doses of pituitrin and insulin, but without ergotamine (Experiment B). The antagonism of pituitrin was clear but did not last long and was not complete, as the dose of insulin was too great to be entirely balanced by 1 c.cm. of pituitrin. No symptoms of hypoglycaemia appeared. On a subsequent day the same dose of insulin was given alone (Experiment C). The blood sugar fell steadily, but not to such a low level as when ergotamine was given, a well known phenomenon.

These experiments seemed to show that ergotamine abolished the antagonism of pituitrin for insulin. This was confirmed in another way with smaller doses of insulin (Table VII, Fig. 2). In Experiment A, 1½ units were given alone, and this proved to be a dose which caused a moderate fall of blood sugar which was followed later by a spontaneous rise. In a second day's experiment (B) 1 c.cm. of pituitrin was given along with insulin. The antagonism of pituitrin was clear and a slight rise of blood sugar occurred, to be followed by a fall when the pituitrin action became enfeebled, as it usually is after one hour. On a third day's experiment (C) 5 mg. of ergotamine was given, and two hours later the same dose of pituitrin and insulin. At first the pituitrin antagonized the insulin, but later the blood sugar fell to a lower level than in B, as always happens when ergotamine has been given to inhibit glycogenolysis. Experiment C was contrary to what we had expected, and contradictory to the results obtained in Table VI. But it was felt that the preliminary rise in blood sugar might simply have been caused by the pituitrin

TABLE VII.—*Effect of Ergotamine on Pituitrin-Insulin Antagonism in a Rabbit.*

(For description see text.)

Time in Minutes.	Experiment A.	Experiment B.	Experiment C.	Experiment D.
—	Insulin alone	Insulin + pituitrin	Ergot 2 hours previously	Ergot 2 hours previously
0	125	136	125	125
0	1½ units insulin	1½ units ins. + 1 c.cm. pit.	1½ units ins. + 1 c.cm. pit.	1½ units ins. + 1 c.cm. pit.
30	98	145	134	158
60	85	130	118	106
90	84	121	92	93
120	84	116	89	71
—	—	—	—	1 c.cm. pit.
150	—	—	81	60
180	—	106	62	59*
210	117	—	—	—

* Symptoms of hypoglycaemia.

FIG. 2.—For description see text and Table VII.

coming into action more rapidly than insulin and producing the initial rise in blood sugar which is the common effect on most rabbits; or, more likely still, that the ergotamine had not yet fully paralysed the sympathetic. Accordingly in Experiment D a second dose of pituitrin was given two hours after the first, when the blood sugar had fallen to a much lower level and there was no doubt that the action of ergotamine was fully established. This second dose of pituitrin had no effect in antagonizing insulin, and the blood sugar continued to fall in the third hour and slight symptoms of hypoglycaemia appeared. Without ergotamine Banting, Macleod, and Burn have shown that an injection of pituitrin invariably abolishes the insulin hypoglycaemia and raises the blood sugar as quickly as an injection of glucose itself.

It seems quite clear from these experiments that ergotamine abolishes the antagonism of pituitrin to insulin.

Evidence that Pituitrin can Cause Glycogenolysis and Reduced Carbohydrate Tolerance.

The above experiments with ergotamine show that this drug abolishes the usual antagonism of pituitrin to insulin. Since ergotamine acts by paralysing the sympathetic and preventing glycogenolysis, we can conclude that pituitrin counteracts insulin by mobilizing sugar from the glycogen of the liver or muscles or both. We look upon the experiment on the diabetic (Case D, Table IV) as affording confirmatory evidence of this. His carbohydrate diet, his blood sugars, and hence his glycogen and carbohydrate stores, were lower than in the other diabetics, and pituitrin antagonized insulin only very slightly. We look upon him as being in much the same condition as an ergotaminized rabbit—that is, unable to mobilize glycogen because he had none in store. The experiment on the case of diabetes insipidus points to the same thing. When he was deficient in pituitrin his carbohydrate tolerance and his power of storing glycogen were very high. After a dose of pituitrin his carbohydrate tolerance, though still very high, was definitely less. It was not possible to try the effect of a large dose of pituitrin on his blood sugar curve because he

developed these curious symptoms already described even with a small dose of 0.75 c.cm.

The clinical evidence of disease due to an enlarged and overactive pituitary gland is of the same nature. In acromegaly the blood sugars are commonly raised, the carbohydrate tolerance reduced, and we may presume that glycogenolysis is excessive. At first the fasting blood sugar is normal, but later all the features of a true diabetes mellitus may develop, presumably by prolonged overstrain of the pancreas. Certainly, it is the anterior lobe which is supposed to be especially affected in acromegaly, and which has been looked upon as influencing carbohydrate metabolism. But it seems clear from our experiments that posterior lobe extracts (pituitrin) do affect carbohydrate metabolism. No clear separation of the functions of the two parts of the gland can be made with our present knowledge.

Evidence that Lack of Pituitrin Causes Excessive Glycogen Synthesis.

The only evidence we have been able to produce of this is the very high carbohydrate tolerance of the above case of diabetes insipidus. But in addition it is generally accepted that deficiency disease of the pituitary, Fröhlich's syndrome, etc., is accompanied by a markedly increased carbohydrate tolerance.

Evidence that Pituitrin can Prevent Glycogenolysis.

Although this is directly contrary to the action of pituitrin already described, there is clear evidence that it can act in this way. Stenstrom¹ was the first to show that large doses of pituitrin inhibit the hyperglycaemia and glycogenolysis caused by adrenaline and anaesthetics. This has been confirmed by Burn and others. Similar evidence is afforded by some observations of Falta⁴ on the effect of adrenaline on the glycosuria of acromegaly. He records two cases in which the patients showed abundant glycosuria after carbohydrate food, but an injection of adrenaline failed to produce any glycosuria.

There is evidence to suggest that when insulin hypoglycaemia is proceeding too far, recovery is aided by an increased production and liberation of adrenaline in the body, which causes a mobilization of glycogen and a rise in blood sugar concentration. In view of Stenstrom's experiments it does not seem likely that when pituitrin antagonizes insulin it does so by calling this protective adrenaline into play.

From all the above evidence it seems that pituitrin plays a complicated part in the regulation of blood sugar and carbohydrate metabolism. It seems to have a balancing action on carbohydrate metabolism and inhibits the action of drugs which tend to change the blood sugar concentration away from normal in either direction. It controls both the hypoglycaemia of insulin and the hyperglycaemia of adrenaline, but it effects no appreciable change on a normal blood sugar concentration.

The Similar Effects of Thyroid and Pituitary on Carbohydrate Metabolism.

It is interesting to note the great similarity of action of these two glands and their extracts, both experimentally and in the clinical evidence of disease. Both have marked effects on total metabolism as judged by the basal metabolic rate, which is increased or diminished respectively by excess or deficiency of both glands. Thyroid feeding in animals empties the glycogen store, raises the blood sugar, and inhibits insulin action to a marked extent.⁵ In hyperthyroidism (Graves's disease) we commonly find raised blood sugars and diminished carbohydrate tolerance, as shown by the response to a glucose meal. As already pointed out by one of us in another publication,⁶ it is very common to find a very low fasting respiratory quotient, which is taken as evidence that the carbohydrate stores of the body are deficient and the body is drawing on protein and fat. The power to oxidize carbohydrate is not defective, for the respiratory quotient rises very high after a carbohydrate meal in these hyperthyroid cases. The clinical picture of hypothyroidism and hypopituitarism is also very similar. Indeed, all the metabolic features of excess and deficiency disease of the two glands are almost the same, and we are

inclined to attribute them primarily to the disturbance of carbohydrate metabolism, and especially to the upset of normal glycogenic function. Many investigators have pointed out effects that disease and extirpation of the thyroid have on the morphology of the pituitary gland, and vice versa, but no constant changes have so far been established.

Does Insulin Antagonize Pituitrin?

There is no clear evidence on this point. We have been struck with the tendency common in diabetics on insulin treatment to become obese on very low diets, sometimes less than 20 calories per kilogram of body weight, but it is rather drawing a bow at a venture to attribute this to inhibition of normal pituitary function. We have heard, however, of a male insulin case who is developing more definite symptoms of hypopituitarism—deposition of excessive fat round the abdomen and buttocks and the loss of pubic hair. We have unfortunately not been able to get in close touch with the case up to the present. The similarity of the appearance of many insulin cases to that of hypopituitarism was noted early by several clinicians in America.

One of us has produced evidence that insulin has a remarkable effect in controlling and ameliorating certain cases of Graves's disease,⁶ and other investigators have observed the same effect. In the same way we believe that insulin might affect acromegaly favourably and prove useful in its treatment, but so far we have not had a suitable case of active acromegaly on which to try it.

Conclusions as to the Effect of the Pituitary on Carbohydrate Metabolism.

Any conclusions we draw are put forward very tentatively. It would seem that the pituitary has a powerful stabilizing influence on blood sugar and carbohydrate metabolism. There are two well recognized mechanisms which control and affect blood sugar concentration. The first is the mechanism which produces varying amounts of endogenous insulin to keep the blood sugar normal by balancing the carbohydrate of the food. It is clearly anabolic in function. The second is the immediate action of adrenaline in raising the blood sugar by mobilizing glycogen to meet any extraordinary needs of the individual for sugar. This mechanism is clearly katabolic. Pituitrin has no definite immediate action on blood sugar, but it controls and compensates the excessive action of the other two substances, tending to keep the blood sugar normal and at an optimum for the individual. These are the facts. But the explanation of how pituitrin can at one time stimulate glycogenolysis and at another inhibit it, as it appears to do, remains a complete mystery. It may be dangerous to deduce the normal action of an internal gland from the effects produced by its extracts, but where the pituitary is concerned the evidence of disease points to the same conclusions. We would suggest that in normal metabolism the pituitary gland, like the thyroid, maintains a balance between anabolism and katabolism. When the gland is upset in either direction an unbalanced condition of metabolism follows, and the first manifestation of this, perhaps the primary cause of all the other metabolic changes, is the upset of the glycogenic regulation of carbohydrate stores and blood sugar concentration.

SUMMARY.

1. Subcutaneous injection of therapeutic doses of 1 c.cm. of posterior lobe extract (pituitrin) have no appreciable or constant effect on blood sugar concentration in normal and diabetic individuals.
2. These doses markedly antagonize the effect of insulin on blood sugar, both in normal persons and diabetics. Experiments with ergotamine show that this antagonism is produced by the mobilization of glucose by pituitrin.
3. The insulin tolerance of normal individuals in the fasting condition is about 15 to 20 units. Much more can be tolerated when insulin is balanced with food.
4. Curious symptoms caused by therapeutic doses of pituitrin in normal individuals are described.

5. Blood sugar experiments on a case of diabetes insipidus are described and their significance is discussed.

6. It is suggested that the pituitary gland, like the thyroid, is one of the most important factors in producing a normal balance between anabolism and katabolism and does so primarily by its effect on glycogenic function and carbohydrate metabolism.

REFERENCES.

- ¹ Burn, J. H.: *Journ. of Physiol.*, lvii, No. 5, 1923. (Consult this for other references.) ² Partos and Katz-Klein: *Zeit. f. Exper. Med.*, xxv, 98, 1921. ³ Lawrence, R. D.: *BRITISH MEDICAL JOURNAL*, March 22nd, 1924. ⁴ Falta: *Endocrine Diseases*, third edition, p. 278. ⁵ Burn and Marks: *Proc. Phys. Soc.*, June, 1924. ⁶ Lawrence, R. D.: *BRITISH MEDICAL JOURNAL*, October 25th, 1924.

ON THE TREATMENT OF CONVERGENT CONCOMITANT SQUINT.

BY

A. FREELAND FERGUS, M.D., F.R.F.P.S.G., LL.D.,
CONSULTING SURGEON, GLASGOW EYE INFIRMARY.

SINCE the meeting of the International Ophthalmic Congress in Edinburgh in 1883 I have always adopted, as a general plan of operative procedure, advancement instead of tenotomy, and on more than one occasion I have ventured to say that tenotomy in ordinary circumstances amounts to malpraxis. It is certainly to Dr. E. Landolt that we owe this changed point of view. Forty years ago he pointed out, in numerous writings and later in a small monograph on the muscles of the eyeballs, the unreasonableness of tenotomy. Strabismus does not depend on overaction of the convergence, but on a defect in the action of the external recti muscles, due no doubt to a fault in the innervation. Landolt has conclusively shown that there is no overaction of the internal recti—that the error is one of impaired latent divergence.

The definition I always gave to the students who attended my instruction was: When the axes of vision do not intersect at the point of fixation, then there is squint. This definition includes all possible cases of squint, and, when properly interpreted, includes also the various forms of heterophoria.

In concomitant convergent squint the axes intersect, if they are in the same horizontal plane, at some point nearer than the point of fixation. If they are not in the same horizontal plane they cross each other somewhere nearer than the point of fixation. One of the characteristics of the variety of squint under consideration is that for almost any point of distant fixation within the field of vision the angle between the two axes is a constant; thereby differing materially from the forms of squint due to muscular paralysis and from those other cases in which the movement of one of the eyes is impaired by the presence of an orbital growth.

Treatment of convergent concomitant strabismus as it occurs in young children has a twofold object—namely, (a) the functional development of the squinting eye both as regards visual acuteness and as regards binocular vision; (b) the removal of an obvious disfigurement.

To a considerable extent treatment should be determined by the age of the patient and the time which has been allowed to pass from the first appearance of the squint. When the condition supervenes in early childhood, say before the patient attains 3 years of age, immediate treatment is urgently required, for if the eye be allowed to squint for a considerable time amblyopia is definitely and permanently established. The delay of a few months inevitably means that the eye is rendered permanently amblyopic. Such patients form an important group which should receive very special attention.

If the onset of true strabismus does not take place till the fifth year or later, it is generally found, if the eyes be otherwise healthy, that each eye is possessed of good visual acuteness. The cases forming this group are few; they border very closely on esophoria, and treatment has