Control of Ingested Carbohydrate by P.I.

The above experiments show that when P.I. is controlling or even reducing endogenous sugar it deals remarkably poorly with ingested carbohydrate and fails to prevent a relatively enormous increase in blood sugar. The Danish workers^{1, 2} have recognized this, and in cases in which they give P.I. at night have been forced to give I. before a carbohydrate breakfast to obtain that full control of hyperglycaemia and glycosuria which is their ideal. We have tried, without observing much difference, in several other experiments to see whether P.I. at different stages of its absorption—that is, half an hour or four hours after injection—can obtain better control over the uniform 50 grams of carbohydrate used. It is very poor in this respect compared with I. An experiment in Table IV shows this clearly with large doses of prota-

TABLE IV

Time	—	Blood Sugar in mg. per 100 c.cm.	
		Arterial	Venous
8.30 a.m.	32 P.I.	132	—
10.0 a.m.	50 grams carbohydrate	102	101
11.0 a.m.		296	264
noon		278	275
1.0 p.m.		183	178

mine in full action. It also shows a comparison of simultaneous arterial and venous blood-sugar values, which are agreed to be an index of sugar utilization by the tissues.

After carbohydrate food in a normal person, or after injection of a large dose of insulin in a diabetic, the venous blood contains far less sugar than the arterial, and the arterio-venous difference should be as much as 20 to 80 mg. per 100 c.cm. We consider that the arterio-venous difference in this experiment is very slight, and reveals little evidence of peripheral activity of P.I. However, when large enough doses of protamine insulinate are given to maintain a very low blood sugar (40 to 60 mg. per 100 c.cm.) fairly liberal amounts of carbohydrate (50 grams a meal or 170 grams a day) have been well tolerated without a rise in blood sugar above 150 mg. and without production of glycosuria. We have been able to control Case I on a liberal amount of carbohydrate (170 grams) with two doses of P.I.: this patient had frequent bouts of glycosuria and persistent ketonuria with oscillating blood sugars on three doses a day of ordinary insulin.

The Occurrence of Hypoglycaemia

We have found, like other observers, that P.I. is much less likely than I. to cause hypoglycaemic symptoms at the same or even lower concentration of blood sugar, doubtless because the rapidity of the fall of blood sugar, as well as its absolute value, is an important factor. We have observed, however, one severe hypoglycaemic attack after P.I., while mild symptoms, at least, are apt to appear if big enough doses are given to attempt to control the hyperglycaemia and glycosuria which result from any reasonable carbohydrate meal. Such attacks occur many hours after carbohydrate meals, and are mostly to be expected between 3 and 6 a.m.

Clinical Conclusions

These clinical experiments amplify and confirm previous published experiences, and permit of the following conclusions.

1. Protamine insulinate acts more slowly and for a much longer period than ordinary insulin, and a large dose can act for more than two days.

2. It is much weaker in dealing with carbohydrate food and usually cannot prevent hyperglycaemia after meals. In contrast, its action on endogenous sugar is nearly as rapid and good as ordinary insulin.

3. It causes less symptoms of hypoglycaemia than ordinary insulin, even at the same blood-sugar concentration. Protamine insulinate is certainly absorbed more slowly from the subcutaneous tissues. It therefore has qualities which promise great use in severe diabetics with oscillating blood sugars and rapidly recurrent ketosis. On the other hand, it is not strong enough in its action to control ingested carbohydrate, so that the use of ordinary insulin before carbohydrate meals and protamine insulinate in the evening has been advocated and is necessary to obtain full control of the diabetic condition.

Another insulin preparation combining the qualities of ordinary and protamine insulinate would obviously be more useful than either, and it is not too much to hope that the Danish or other experimenters may soon obtain this. In the meantime, it must be stated that protamine insulinate, great though its advantage may be in some cases, is not generally obtainable for clinical use in this country, and is indeed still in the experimental stage.

A DISCUSSION OF INSULIN ACTION

BY

R. D. LAWRENCE

Deductions from Experiments with P.I.

From the above experiments with protamine insulinate we can distinguish two different phases of insulin action in the severe diabetic. A low concentration of insulin in the tissues, such as P.I. gives, is able to control hyperglycaemia from endogenous sources for long periods, but is quite incapable of coping with ingested carbohydrate as the higher concentrations of ordinary insulin do. I conclude that in normal carbohydrate metabolism a continuous small secretion from the pancreas (or perhaps merely a small residue from the last active secretion) controls the blood sugar continuously, but that a large extra secretion must be produced by the pancreas by the stimulus of ingested carbohydrate to deal with this successfully. Such an increased secretion of insulin in response to a rising blood sugar is a point of view which has been suggested before, but it has never been satisfactorily proved. Indeed, several experiments, especially recent ones by Soskin on depancreatized dogs, cast serious doubt on it.

Another most interesting observation, shown in detail in Table II, is the return of a heavy ketonuria from the thirty-seventh hour after P.I., at a time when the glycaemia was still completely controlled. During this time the patient was not in a typical diabetic condition, and the ketosis is comparable to that which ensues from carbohydrate starvation in normal individuals and is supposed to coincide with the exhaustion of liver glycogen. Whether her ketosis (occurring twenty-six hours after the last carbohydrate meal) coincided with glycogen depletion or was partly due to the protein and fat meals we cannot know for certain, but it did not develop until ten hours after the first protein and fat meal. This type of starvation ketosis is generally agreed to result from the accumulating by-products of protein and probably fat katabolism during the process of neoglucogenesis in the liver.

In a normal starved person the injection of insulin alone does not remove the ketosis (Goldblatt), but carbohydrate food rapidly does. In the severe diabetic investigated with ordinary "short-action" insulin hyperglycaemia and ketosis disappear and recur almost simultaneously, and it is difficult to define and study the two conditions separately. But protamine insulinate has revealed a condition in which ketogenesis is not checked, presumably because neoglucogenesis is proceeding as in starvation, and yet the new sugar does not cause hyperglycaemia. I would conclude that the small concentration of P.I. fixes the new sugar, probably as glycogen, but does not stop the new production.

Diabetes and Insulin Action

I am tempted, in the light of the above observations, to try to discuss the complicated problem of how insulin acts and what pancreatic diabetes is. Severe diabetes has presented two main aspects to most observers: (1) the failure to utilize (store and/or burn) carbohydrate; and (2) the over-production of new sugar and ketones even in starvation.

Whether the second aspect is a primary defect or merely secondary to the first has been variously debated. Insulin rectifies both defects for a time, but it has been argued whether it checks the over-productive neoglucogenic process directly or merely makes the latter unnecessary by providing sufficient utilizable carbohydrate. I have always inclined to the latter view, as it is unlikely that a definite chemical substance such as insulin does more than one thing. I suggest that the only action of insulin is to turn glucose into glycogen in both liver and muscles.

Since the days of Claude Bernard the main interest in diabetes has always centred not only on the sugar in the blood but also on the glycogen in the tissues. A few clear facts emerge from thousands of experiments. It is certain that the diabetic liver contains practically no glycogen, and that muscle glycogen is diminished. Insulin and sugar make these normal in the diabetic dog, but in normal animals contradictory effects have been observed. It is generally agreed that in the skeletal* muscles insulin always increases glycogen until the convulsive stage, in which it is reduced, as might be expected, by the violent contractions. In the liver, however, insulin has been shown to have varying effects, depending on the previous nutrition, the species and age, and the duration of its action. In most experiments glycogen is reduced, but is sometimes unchanged and occasionally increased. If insulin merely turns glucose into glycogen we would expect no increase in the liver unless much sugar were present for it to act on; and as insulin seems to favour the muscles in its deposition of glycogen from sugar, we might expect it to deplete the liver, especially after a few hours' action, which has been found to happen.

The Supply of Blood Sugar

New sugar for the body's needs comes from two sources: (1) ingested carbohydrate; and (2) new production from the intermediate metabolism of protein and, probably, of fat.

1. The absorbed sugar from ingested carbohydrate is turned into glycogen by insulin, whose function I consider this to be. It has always seemed significant to me that the islets of Langerhans are buried in the largest digestive gland in the body. The rising blood sugar after food stimulates an increased production of insulin, which stores the excess sugar as glycogen primarily in the muscles and also in the liver when large enough amounts of sugar are available. There is also a small secretion between meals, to keep the blood sugar normal all the time. There is

so little secretion in severe diabetics that hyperglycaemia is present even in starvation. However, injections of protamine insulinate can supply for long periods sufficient insulin to control hyperglycaemia except after meals. The mild diabetic lives in a similar condition, and has sufficient endogenous insulin to prevent hyperglycaemia except after much carbohydrate food.

2. When no carbohydrate food is available, or during complete starvation, the blood sugar does not fall very appreciably below the fasting level, and can be maintained for weeks in the absence of food, obviously by the production of new sugar from endogenous sources. This new sugar can be produced only from protein and fat,* and the production is always accompanied by the onset of ketosis, which I look upon as a sure indication that transformation of protein and fat to new sugar is in progress. It seems certain that the liver is essential for this transformation, because in hepatectomized dogs the blood sugar falls to a fatal low level and ketosis never develops. In the normal starved individual neoglucogenesis produces ketonaemia but not hyperglycaemia, because the new sugar is stored as glycogen by insulin. But in the severe diabetic, unable to store glucose as glycogen, neoglucogenesis produces both ketonaemia and hyperglycaemia, and the latter may be so marked that the new sugar production has been mistaken for the primary defect in diabetes—the "over-production" theory. However, we have seen from the protamine insulinate experiment that the presence of a small concentration of insulin in a severe diabetic can entirely control hyperglycaemia without stopping ketosis and neoglucogenesis, which proceed exactly as in a normal starved person. Neoglucogenesis is directly dependent neither on insulin nor on appreciable changes in the blood-sugar level, but, I suggest, on the concentration of liver glycogen.

The Adrenal, Thyroid, and Pituitary Glands

The action of these three endocrine glands and their extracts must also be considered in the regulation of blood sugar and in the diabetic picture. In excess, both when administered experimentally and in human disease, these glands are antagonists to the hypoglycaemic action of insulin, and all have recognized effects on liver glycogen. In the normal animal adrenaline mobilizes liver glycogen into blood glucose within an hour; thyroxine entirely prevents the deposition of liver glycogen, however much carbohydrate is taken; and anterior pituitary extracts make liver glycogen very labile and unstable, whereby the hyperglycaemia after adrenaline is increased and the hypoglycaemia after insulin is diminished. Indeed, injections of pituitary extracts can produce in the experimental animal a condition of glycosuria and ketonuria very like pancreatic diabetes. On the other hand, removal of the pituitary produces great sensitivity to insulin injections and sometimes a fatal spontaneous hypoglycaemia comparable with the effects of hepatectomy. Also, in the absence of the pituitary, diabetes does not develop in dogs when the pancreas is excised. The removal of the suprarenal has similar effects.

It would appear that the above three glands, whatever their exact individual share may be, play an important part in the supply of blood sugar. In excess they facilitate the supply of peripheral sugar by preventing the deposition of liver glycogen, and, when they are defective, the resultant hypoglycaemia may be caused by the undue stability of liver glycogen. It may also be that, apart from their effect on liver glycogen, these glands directly stimulate the katabolism of protein and fat involved in the neoglucogenic process, perhaps by reflex overactivity, when new sugar is necessary. This would be a useful function—but this is mostly surmise, although there is

* It appears that the glycogen of the heart and unstriated muscle behaves quite differently in diabetes and after insulin, and is not included here.

* The latter is still disputed by some physiologists.

some evidence for it. For instance, the pituitary is known to affect protein and fat metabolism, and the adrenal is certainly hypertrophied in starvation. If they do become overactive some curious clinical observations mentioned below find an explanation.

On the clinical side the condition of "resistance" to insulin in diabetics with Graves's disease is explained by the action of thyroid on liver glycogen. I would also suggest that the "diabetic" blood-sugar curves observed in normal people after carbohydrate starvation, and the reduced action of insulin in normal people and in diabetics on low carbohydrate diets (the insulin "insensitivity" so neatly demonstrated by Himsworth), may be due not to the absence of an "insulin-kinase," but to the prevention of glycogen deposition associated with the neoglucogenic process and probably dependent on overactivity of the adrenal, thyroid, or pituitary. Again, the puzzling fact that low-carbohydrate high-fat, and high-carbohydrate low-fat equicaloric diets require much the same dose of insulin in severe diabetics can also be explained. On low carbohydrate diets the body has insufficient sugar supplied and new sugar production takes place, requiring insulin for its control. Clinically the action of insulin is strikingly quantitative, and I think it likely that one unit of insulin is required to turn an equal amount of glucose into glycogen, whether the former is exogenous or endogenous in origin.

The Liver and Its Glycogenic Function

The theory presented in this paper requires the hypothesis of an automatic mechanism in the liver, dependent on a critical concentration of liver glycogen, as regulating blood sugar and, especially, new sugar production. I would postulate a glucose-glycogen equilibrium, as inherent as the heart-beat, though probably affected, as the latter is, by sympathetic and parasympathetic influences.

The mechanism of pancreatic insulin to deal with ingested sugar by turning it into muscle and liver glycogen is easy to understand. After sufficient carbohydrate food endogenous sugar production is stopped and the respiratory quotient approaches unity. As sugar is burned in the tissues liver glycogen is paid out as glucose to maintain an adequate blood sugar for peripheral needs, and a low critical concentration of liver glycogen is reached which calls for new sugar production and initiates the neoglucogenic process. A low respiratory quotient and ketosis are signs of this. Insulin *per se* does not inhibit the process, but is necessary for the new sugar to be turned into liver glycogen. In the absence of insulin to re-form a critical concentration of liver glycogen the neoglucogenic process runs riot, hyperglycaemia persists, and, more serious still, the diabetic is threatened by severe ketosis from the by-products. I think that the time-honoured phrase "the glycogenic function of the liver" is confusing, and suggests one process where two should be distinguished: *first, the synthesis by the liver of new glucose from protein and fat, from circulating lactic acid, etc., and, secondly, the formation of liver glycogen from this sugar by the action of insulin.*

This theory, outlined in main principle only, fits in with most of the definite experimental findings, and certainly with the clinical manifestations of diabetes and insulin action, with which I am more familiar. It gives me a clear point of view (at least temporarily!) in the approach to clinical problems, and I therefore make no apologies to the physiologists for incursions into their sphere.

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Clinical Memoranda

Allergy in Five Generations

Most authorities are agreed that heredity plays an important part in the aetiology of the various allergic diseases and of asthma in particular, and the following pedigree, which traces these conditions through five generations, appears to be of importance in confirming this view and in demonstrating how different forms of allergy are found in different members of an affected stock.

I have had the opportunity over a period of years of observing this family group, in which allergic conditions occurred in both ancestral lines, and the underlying sensitiveness or metabolic error appears in each of nine brothers and sisters (fourth generation) in different forms and degrees, many showing several varieties of the dyscrasia. Three members of this group (a mother and two daughters) have rheumatoid arthritis in addition to other allergic manifestations. This is a condition sufficiently uncommon to make such a distribution remarkable, and it supports the theory of the allergic nature of this disease. It is too early to know how the fifth generation will be affected; most of them are still children, and one is known to be asthmatic. Although Bray states in *Recent Advances in Allergy* that where there is allergic inheritance symptoms tend to appear early (before 6 years of age if inheritance is bilateral, before 8 if unilateral), yet some members of this family did not show signs of allergy until the age of 35 or 40.

Generation I: Asthma.

Generation II: Hay fever.

Generation III: 1. Asthma.
2. Food allergy.
3. Asthma, hay fever, rheumatoid arthritis.
4. Died aged about 14 years (no allergy known).
5. Migraine.
6. Food allergy.

Generation IV: 1. Asthma.
2. No allergy known.
3. Migraine and hay fever.
4. Hay fever, train sickness.
5. Asthma, hay fever, rheumatoid arthritis.
6. Vasomotor rhinorrhoea.
7. Migraine, train sickness, food allergy.
8. Food allergy, urticaria, rheumatoid arthritis.
9. Asthma (first attack about 40 years of age).
10. Migraine, asthma, vasomotor rhinorrhoea.
11. Hay fever, food allergy.

Generation V: 2. Asthma, vasomotor rhinorrhoea, car sickness.

Such allergy as is shown here may be understood to imply a chemical dyscrasia of metabolism, probably of the nature of an inefficiency in the breaking down of certain proteins causing a condition the opposite of assimilation (or the opposite of immunity, as another writer has expressed it), leading to lesions which are essentially similar in the different organs attacked—that is, a vasomotor disturbance, with capillary dilatation and increased permeability of the vessels, transudation into the surrounding tissues, and exudation. Thus in asthma the bronchioles are affected, in hay fever the nasal mucosa, in migraine the meninges or ependyma, in urticaria the skin, and in rheumatoid arthritis the muscles, bones, and joints.