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Review Articles

Diabetes: The Genetic Connections*

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Summary. Insulin dependent (IDD) and non-insulin dependent diabetes (NIDD) are separate disorders. Twin studies show that IDD cannot be entirely due to genetic causes as concordance is no more than about 50%, but there is some inherited predisposition to it as shown by HLA patterns. NIDD, on the other hand, is predominantly due to genetic causes since identical twins are nearly always concordant. Many cases of NIDD show chlorpropamide alcohol flushing (CPAF), a dominantly inherited feature which may precede the appearance of diabetes and thus act as a genetic marker for this type of diabetes. Diabetics who show chlorpropamide acohol flushing are less likely to develop retinopathy than those who do not. Genetic factors must therefore affect the incidence and severity of diabetic retinopathy. Chlorpropamide alcohol flushing is due to sensitivity to enkephalin. Enkephalin and other opioids affect carbohydrate metabolism and insulin release. It is possible therefore that they act as neurotransmitters and cause NIDD by a sympathetically mediated effect on the liver and pancreas – in other words, that as far as NIDD is concerned Claude Bernard's views on the cause of diabetes may have been right.

Key words: Genetics, identical twins, chlorpropamide alcohol flushing, retinopathy, enkephalin, piqûre, insulin dependent diabetes, non-insulin dependent diabetes.

Our knowledge of the genetics of diabetes has for long been confused because diabetes has been regarded as a single disease. When its two main forms are studied separately we can learn much about their aetiology, especially what is and what is not inherited.

In this lecture I review Claude Bernard's contribution to the history of diabetes, then put forward six propositions concerning the genetics of diabetes and its complications. I then try to answer two questions raised by these propositions. Finally, I conclude that the work of Claude Bernard is even more relevant today than it was 130 years ago and that his observations provide the basis for a theory of the causation of non-insulin dependent diabetes.

Claude Bernard and the History of Diabetes

In preparing this lecture I have read Claude Bernard's writings on diabetes, at first out of homage to his genius, then with increasing fascination as it became clear that his studies are still so important. Unfortunately Claude Bernard's Introduction to the Study of Experimental Medicine [1] is the only one of his books to have been translated into English (apart from his notebook Cahier Rouge). Great though this book is, in particular its revelation of his attitude to experimental science, it is of less value to those interested in diabetes than Leçons sur le diabète [2] and Leçons de physiologie [3]. These two volumes, especially the second, are a feast for anyone interested in diabetes.

Why did Claude Bernard do his piqûre experiments; did he expect that piqûre would lead to diabetes, and if so why, or was it an incidental observation?

These questions seem also to have troubled Claude Bernard's contempories: "I have been asked" he wrote five years later [4] "and indeed still am, how I was led to the extraordinary discovery that

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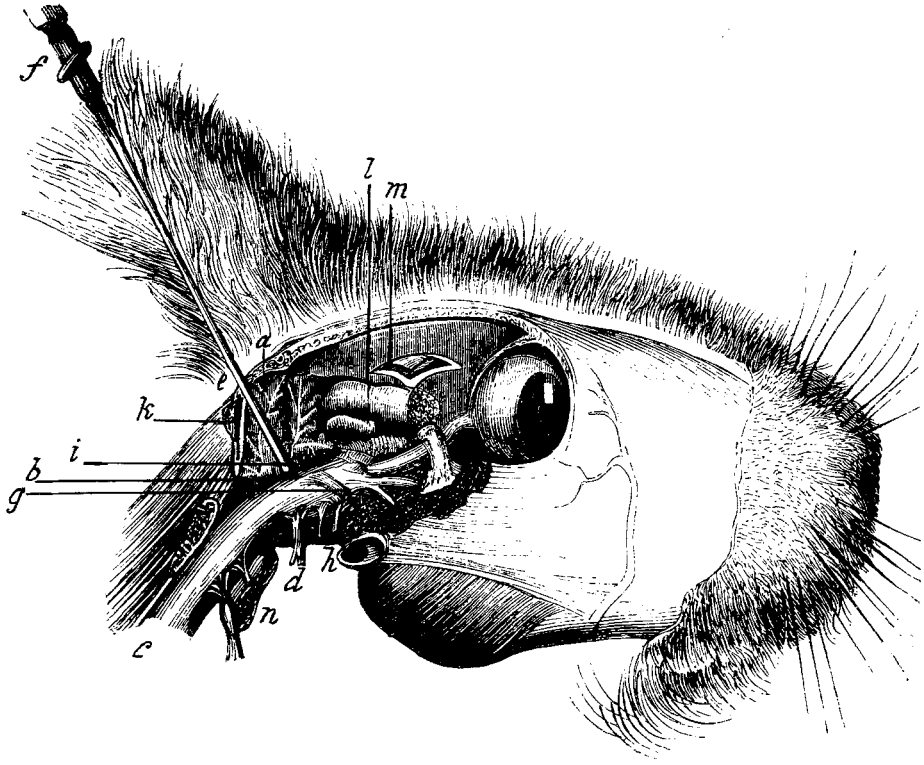

Fig. 1. Claude Bernard's illustration of piqûre [5]. The instrument penetrates the floor of the 4th ventricle in the midline at a level between the 8th and 10th nerve nuclei

an animal can be made diabetic by pricking a particular part of the nervous system." He then goes on to show that it was not the result of a happy chance but, as one might have expected, of logical and brilliant reasoning.

"I had already observed that the liver was a secretory organ, producing a sugary substance, and it was already known that the nervous system influences all secretory organs to increase or decrease their secretions. M. Magendie had observed that stimulation of the lachrymal branch of the trigeminal nerves produced copious tears, and that section of these nerves cuts off the flow.

"I too had observed that sectioning the vagus of an animal, as I showed in one of the earlier lectures, abolished the secretion of glycogen in the liver. I wanted then to try to produce the reverse effect – an exaggeration of this function. I therefore stimulated the vagus electrically, but was never able to produce the result I had expected. I then remembered that when experimenting on another subject by cutting the 5th nerves in the brain it sometimes happened that, instead of operating at this point, I merely pricked the place where the nerve originated in the brain; then the secretions, which were reduced if the nerve was cleanly cut, were exaggerated, when one injured only the annular protuberance: tears and saliva flowed abundantly.

"The idea came to me that, since I could not succeed in exciting the liver directly by electrically stimulating the vagus, I might, by pricking the root of this nerve, produce an effect analogous to that which I had seen in the secretions which were under the control of the 5th nerves. I therefore exposed the floor of the 4th ventricle, and when I pricked the point at which the vagus arises I succeeded at the first attempt in making the animal diabetic. At the end of an hour, the blood and urine of the animal were full of sugar.

"I believed that the explanation for the appearance of sugar in this experiment was that its secretion was directly controlled by the vagus, and the experiment seemed to confirm my theory. However, I was mistaken, as I learnt later; it is not via the vagus that nervous stimulation results in secretion (of glucose), because if I cut the vagus before pricking the medulla, sugar appeared no less abundantly in the blood and urine. So the effect of the piqûre was not transmitted by the vagus. If the vagus is left intact and the spinal medulla is cut above the origin of the sympathetic fibres which go to the liver, the production of sugar is abolished.

"This led me to examine more closely the influence of the nervous system on secretion and I came to believe that, instead of exerting a direct influence, the effect is almost always mediated reflexly via a sympathetic ganglion. So I had to give up my original theory that the stimulus from the nerve centres went via the vagus to the liver. What actually happens is different: the vagus seems to carry a centripetal

stimulus to the nerve centres, which then descends through the spinal medulla and reaches the liver via sympathetic fibres and ganglia."

In the previous lecture [5] he had explained exactly how he produced the piqûre lesion (Fig. 1). He illustrates the instrument, a narrow probe of about 1 mm. diameter with a bladed point and a strong handle. Holding the rabbit's head firmly in his left hand and getting an assistant to hold the legs he inserted the instrument through the spongy portion of the occipital protruberance into the cranial cavity. He then directed the instrument towards a line joining the two ears. As he says, it is essential to prevent the rabbit from moving its head at this stage of the procedure, and one can see why! He pushed the instrument forwards until he reached the base of the skull then withdrew it. The animal was, as he invited his audience in front of whom he had done the experiment to observe, little the worse for the procedure – except that it was diabetic; within one or two hours sugar appeared in the urine. Piqûre diabetes was always temporary, passing off within a few hours.

The site of the lesion Claude Bernard aimed to produce was in the midline of the floor of the 4th ventricle at a level between the 8th and 10th nerve nuclei but when the lesion was higher or more lateral diabetes was still produced. The same was found by Banting and Best and their colleagues in 1922 when they used piqûre diabetic rabbits to test the value of their newly discovered insulin [6]. Thus lesions in several sites in the floor of the 4th ventricle produce diabetes.

It is ironical that if Claude Bernard were alive today piqûre diabetes would probably not have been discovered. His earlier experiments were done without anaesthesia and must often have involved suffering for the animals. If he had been compelled to use anaesthetics he would probably have found nothing as hyperglycaemia is blocked by general anaesthesia [7].

Claude Bernard made another observation, which seems not to have been noticed, that might also have bearing on the aetiology of non-insulin dependent diabetes. In studying the action of curare he observed that it caused hyperglycaemia and glycosuria [8]. It is difficult to be sure what led him to make this observation, possibly he was impressed by the effect of curare in stimulating the secretion of tears and saliva and it may have been by analogy with this observation, which had originally led him to try piqûre, that he thought of an effect of curare on blood sugar. He showed that the hyperglycaemic effect of curare was not due to muscular paralysis or artificial respiration as it occurred in the absence of both. If the animal had been starved hyperglycaemia was somewhat less[1].

Finally, Claude Bernard noted that morphine in large doses produced diabetes, although he gives little evidence for this statement. He concluded that the mechanisms by which piqûre, curare and morphine produced diabetes were the same, stimulation of hepatic glucose output as a result of increased blood supply to the liver, an effect mediated through its vasomotor innervation.

Six Propositions

These are:

1) Insulin dependent and non-insulin dependent diabetes are distinct entities.

2) Insulin dependent diabetes is not entirely due to genetic causes.

3) Non-insulin dependent diabetes, on the other hand, is predominantly inherited.

4) There is a genetic marker for noninsulin dependent diabetes, chlorpropamide alcohol flushing.

5) Chlorpropamide alcohol flushing is due to sensitivity to the neuropeptide enkephalin.

6) Diabetic retinopathy is, to a considerable extent, due to genetic causes.

1. Insulin Dependent (IDD) and Non-Insulin Dependent Diabetes (NIDD) are Distinct Entities

There is no longer any serious need to argue this proposition. Although some writers still speak of diabetes as if it were a single entity this is unjustifiable. The evidence that insulin dependent (IDD) and non-insulin dependent diabetes (NIDD) are distinct is irrefutable.

(a) They are different histologically. A striking feature of non-insulin dependent diabetes is the comparative normality of the islets compared to IDD where there is insulitis.

(b) If NIDD were due to a degenerative process in the beta cell it would presumably progress leading eventually to insulin dependence, yet this is a rarity; more often these patients can be controlled indefinitely without insulin. This static state in non-insulin

[1] Claude Bernard says that fasting prevents the appearance of experimental diabetes. At first I found this puzzling as he had demonstrated a considerable rise of blood sugar after curare even when the animal was fasting. However, he clearly equates diabetes with glycosuria. He recognises that hyperglycaemia can occur without glycosuria but does not apparently regard this as diabetes. It may be important to keep this small point in mind when reading Claude Bernard's writings

Table 1. Diabetes in identical twins

	Number of pairs		
	Concordant	Discordant	Total
IDD	73	59	132
NIDD	47	6	53
			185

dependent diabetes is in striking contrast to the insulin dependent type where a destructive process affecting the islets leads to complete failure of insulin production.

(c) Islet cell antibodies are commonly found in newly diagnosed cases of IDD, rarely in NIDD [9].

(d) IDD is associated with certain HLA types, whereas NIDD is not [10].

(e) Identical twin studies show widely different concordance rates in the two types (see propositions 2 and 3).

(f) Chlorpropamide-alcohol flushing, an inherited feature, is common in NIDD but rare in IDD (see proposition 4).

The aetiological distinction between insulin dependent and non-insulin dependent diabetes is central to this lecture.

2. Insulin Dependent Diabetes is Not Entirely Due to Genetic Causes

There has for many years been a widespread belief that diabetes is entirely inherited. If IDD and NIDD are aetiologically distinct syndromes they cannot be inherited in the same way; even IDD, which was thought to be the most powerfully influenced by genetic causes, is not due exclusively to them. This point is of some importance not only in understanding the aetiology of IDD but in giving clinical advice to patients who ask about the risks of passing on diabetes to their children. It has further importance in relation to research on "prediabetes". If the pattern of inheritance of diabetes of any type is precisely understood then it may be possible to predict those who will later develop the disease, i. e. to identify "prediabetics." In that case studies of their histological or biochemical features, for example the thickness of basement membrane in muscle capillaries, may give information about the earliest manifestations of this type of diabetes. However, if the genetic basis for the disease is uncertain then such predictions are likely to be erroneous.

The evidence that IDD is not entirely genetic in its origin comes from studies of identical twins. [11, 12, 13, 14, 15]. Our series of identical twins studied at King's College Hospital now comprises 185 pairs (Table 1). These twins have been discovered in our own clinic and through physicians and other colleagues in the British Diabetic Association. The study has been in progress for 13 years and although the number of twins collected is now large the total still represents only a small proportion of the number of identical twin pairs with diabetes which must exist in the British population. We cannot be sure therefore that selective factors have not operated in our ascertainment of these twins, indeed it is highly probable that they have; in particular there is likely to have been some bias towards the ascertainment of concordant as against discordant twins since they have a double chance of recognition. It is difficult to see any counter-bias operating in the opposite direction, i. e. favouring ascertainment of the discordant twin pairs, and it therefore seems highly probable that in our series concordant pairs are relatively over-represented. Nevertheless, nearly half the IDD pairs are discordant, 59 out of 132, i. e. one twin has insulin dependent diabetes and the other is not diabetic (Table 1).

It might be argued that discordance is not a real phenomenon, that the unaffected co-twins of the diabetics will themselves become diabetic. I do not believe that this is true. (a) We have tested the unaffected co-twins repeatedly and there has been no change in glucose tolerance or insulin secretion over the years. In some cases twins have been tested on seven occasions over a period of as long as 13 years and have shown no tendency to develop diabetes; 11 twins are still not diabetic more than 20 years after their co-twins have developed insulin dependent diabetes. (b) In most concordant pairs, the twins have become diabetic at about the same time – within 5 years in two thirds, within 10 years in nine tenths. On the other hand in the discordant pairs a third have gone for more than 10 years since the first twin developed diabetes and the second twin is still not diabetic. It seems highly probable therefore that in many, probably most, discordant pairs in which the first twin has had insulin dependent diabetes for more than 5 years the second twin will remain non-diabetic.

Although insulin dependent diabetes is not entirely due to genetic causes there is nevertheless a genetic predisposition to diabetes in these cases since even the discordant twin pairs show the HLA pattern characteristic of IDD [16, 17]. Whether the predisposition to diabetes is the same in the discordant as in the concordant pairs is still unsure – it depends upon whether the HLA pattern is exactly the same in the concordant and discordant groups. Present evidence from HLA typing at the B locus is inconclusive and we are now studying HLA D and Bf types. If any difference emerges in the concordant and discordant twins it will mean that insulin dependent diabetes consists of two distinct genetic types.

3. Non-Insulin Dependent Diabetes is Predominantly Inherited

As we began to collect these twins we were surprised, although we should not have been, to discover that almost all NIDD pairs were concordant. In about half these cases when we first saw the affected twins their co-twins were thought not to be diabetic but on glucose tolerance testing they were almost invariably found to be abnormal. From the present total of 53 noninsulin dependent twin pairs 47 are concordant and in the discordant pairs the diabetic twin has been diagnosed only within the last 3 years. The interval between diagnosis of diabetes in the two twins of the concordant NIDD pairs has in no case been more than 5 years.

We are dealing here with twins most of whom are over the age of 40 and have been living apart for several decades. If there were any environmental cause responsible for their diabetes one should have found several pairs in which one twin had encountered this cause and the other had not and who were therefore discordant. Even when two twins of a pair are of different weights they are still concordant.

We cannot escape the conclusion that noninsulin dependent diabetes is predominantly, almost entirely, due to a genetic cause.

4. There is a Genetic Marker for Some Cases of NIDD: Chlorpropamide Alcohol Flushing

The phenomenon of facial flushing after alcohol in patients taking chlorpropamide has been known since the drug was first introduced more than 20 years ago [18]. I had long wondered what the mechanism of this flush was and whether it resulted from a single gene effect. A simple event suggested that it was.

We have under our care several members of a family called Mason[2]. Our original patient, Mrs. Jacqueline Mason, was discovered to be diabetic at the age of 12. She is now 48 and although she has had diabetes for 36 years she does not require insulin. Her two daughters were discovered to be diabetic at the ages of 5 and 7 and 15 years later they too are still controlled without insulin. Approximately half the members of Mrs. Mason's family are diabetic and all are controlled without insulin.

Mrs. Mason and her daughters take chlorpropamide. When we discovered that all three experienced facial flushing after alcohol the significance of this reaction was immediately apparent. In order to discover whether the other members of the Mason family who were diabetic also flushed we developed a simple test in which the patient takes a tablet of 250 mg of chlorpropamide and 12 hours later drinks 40 ml of sherry [21]. The test is consistent and repeatable. We applied this test to other members of the Mason family and of other families with a similar type of diabetes. Eighty out of 90 of those who were diabetic showed facial flushing, whereas only two out of 36 of those who were not did so. It was obvious therefore that chlorpropamide alcohol flushing (CPAF) was very closely related to diabetes in these "Mason-type" families. At first we thought CPAF was a marker for "Mason-type" diabetes but when we extended the study to other diabetics we found it occurred in them too, though less often.

That CPAF is genetically determined was confirmed by studies in identical twins [21]. In 17 pairs both twins showed the same reaction to the CPAF test whether they were concordant or discordant for diabetes. We have not seen discordance for CPAF in identical twin pairs.

CPAF is inherited in a dominant manner [21]. The evidence for this is: (a) half the offspring of CPAF cases themselves show CPAF; (b) when parents of patients with CPAF are available for testing one has always been found to show CPAF; (c) we have seen two families with CPAF in three successive generations.

The frequency of CPAF in "Mason-type" diabetes is about 90% and it is high in NIDD generally [21, 22]. Although a frequency of about 33% had previously been reported [18] this is an under-estimate. We have found a prevalence in unselected noninsulin dependent diabetics of about 65%. The figure is higher – 80% – in those cases where there is a first degree family history of diabetes, but even in those without a family history it is still 30%, which is three times as high as in IDD and in the general population. CPAF is therefore strongly associated with NIDD especially when there is a positive family history, and in some families the association is almost complete.

We have tested 20 unaffected offspring of CPAF positive diabetics – 12 flushed and 8 did not. As the older members of these families who show CPAF are diabetic it seems probable that these 12 persons are destined to develop diabetes, i. e. that in these cir-

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[2] We have now collected several other families to add to the three – including family M (for Mason) – originally described from this department by Tattersall [19] and we refer to this type of diabetes, which is mild and non-ketotic, does not deteriorate and can be controlled without insulin, as "Mason-type" diabetes. We prefer this simple term to maturity-onset diabetes of youth [20] (MODY) since it is probable that there are other syndromes in which mild diabetes may be diagnosed in early life. Furthermore "Mason-type" diabetes may not be diagnosed until middle or late life

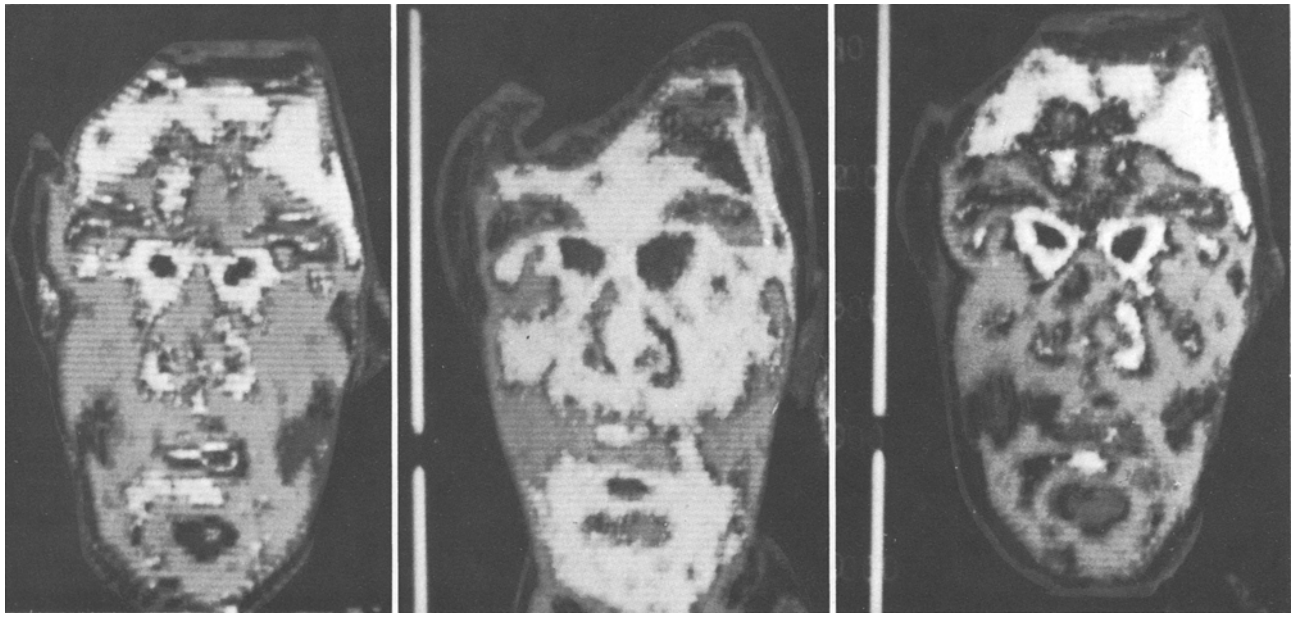

Fig. 2. Chlorpropamide alcohol flushing is abolished by naloxone. Black and white representation of thermogram (in which hot parts of the face are shown by the pale areas) taken before (left) and after (centre) drinking 40 ml sherry. If naloxone is infused no change of temperature occurs after alcohol (right). (Taken with kind permission from [24])

cumstances CPAF is a genetic marker. It is too soon to be sure how reliable a marker it will prove to be; we have seen a family in which a woman showed CPAF, as did her mother and her daughter; they were diabetic but she was not. We estimate that the child of a CPAF positive diabetic who himself shows CPAF has a 70 times increased chance of developing NIDD.

We think that it is now possible, as it has not previously been, to identify with considerable, although not complete, confidence a prediabetic of the non-insulin dependent type.

5. Chlorpropamide-Alcohol Flushing is Due to Sensitivity to Enkephalin

R. D. G. Leslie and I presented our findings in relation to CPAF at a meeting of the British Diabetic Association in April 1978. At that meeting was Dr. W. A. Stubbs who with his colleagues had been studying the endocrine effects of an infusion of an enkephalin analogue [23]. Stubbs had noted that when he received an infusion of this material he showed facial flushing which was much more intense than in any of the other experimental subjects. He wondered whether this reaction could be in any way related to CPAF and when he told us that his father was a diabetic who showed CPAF it was obvious that we had been given a very strong clue.

There were two ways of testing the notion that CPAF might be due to the effects of enkephalin, a) to block it with an antagonist b) to reproduce it. The results were clear-cut [24]. If patients who showed CPAF were given an infusion of the specific opiate antagonist naloxone before taking the alcohol and for 25 minutes afterwards the flush was abolished (Fig. 2). If the enkephalin analogue DAMME (D-Ala^2, MePhe^4 (O)-o) enkephalin (Sandoz, Basel, FK 33824) was injected intravenoulsy those who showed CPAF had marked facial flushing whereas those who did not show CPAF did not (Fig. 3). There was a clear distinction between the response of CPAF positive and negative subjects, none of the former showing a skin temperature rise of less than 1 °C and none of the latter more than this amount. We concluded from this that the chlorpropamide alcohol flush was due to increased sensitivity to enkephalin.

Sensitivity to enkephalin is likely to be a central rather than a peripheral effect. If enkephalin is pricked into the skin of the forehead and forearm little reaction is seen. There is a small flush at the site of injection in the forearm which is seen in both those who are CPAF positive and those who are negative but virtually no reaction in the forehead. This is in distinction from CPAF where the flushing and rise of skin temperature is confined to the face and neck and there is no change in skin temperature in the forearm.

6. Diabetic Retinopathy is, to a Considerable Extent, Due to Genetic Causes

A striking feature of Mason-type diabetes is its mildness, both in its treatment and in its relative freedom from complications [19]. Many of these patients show no diabetic retinopathy after several decades. When it appears retinopathy is mild and proliferative retinopathy is rare. This suggested to us that there might be a connection between CPAF, which is so common in Mason-type diabetes, and a freedom from retinopathy in non-insulin dependent diabetics generally.

This has subsequently been confirmed. Complications are much less common in non-insulin dependent diabetics who show CPAF than in those who do not and, when present, the complications are usually mild [25]. Severe diabetic retinopathy is seven times commoner in CPAF negative than in CPAF positive cases (Fig. 4). Among 191 CPAF diabetics with a mean duration of diabetes of 11 years only one was blind from diabetic retinopathy compared with 8 of 100 CPAF negative cases of similar duration.

This must mean, since CPAF is inherited, that the tendency to develop diabetic retinopathy, and by analogy other microvascular complications, is also inherited.

There is further evidence of a genetic component in the aetiology of diabetic retinopathy from the twin studies [26]. Amongst insulin dependent twin pairs retinopathy is commoner in the concordant pairs than in the diabetic twins of discordant pairs. Furthermore, retinopathy is not seen in the unaffected twins of discordant pairs. In the concordant pairs both twins show a remarkable similarity in the development of retinopathy. Its time of appearance and severity is usually the same in both twins. Progression of retinopathy seems to relate to the time of onset of the diabetes. Thus the retinopathy in the second twin may be less severe than in the first but of comparable severity to that which was found in the first twin at the same time after the onset of diabetes. In some of our pairs we have been able to observe the second twin following in the footsteps of the first in the development of retinopathy. This suggests that the triggering mechanism for the development of retinopathy results from hyperglycaemia, or some other feature of the diabetic state, but that the tendency to develop retinopathy and its progression is then largely influenced by the genetic background of the patient.

I do not wish to enter here into the controversy concerning the value of "good" diabetic control in preventing the development of diabetic complications – many reputations have been lost in the attempt! However, good control cannot be the whole answer, there must be a genetic component in the aetiology of diabetic retinopathy – and presumably of the other microvascular complications. Interesting and important though this observation may be it should not lead one to abandon the attempt at good diabetic treatment. Although CPAF positive cases are less likely to develop retinopathy, especially severe retinopathy, they still can do so and it is for this reason, as well as on humanitarian grounds, that

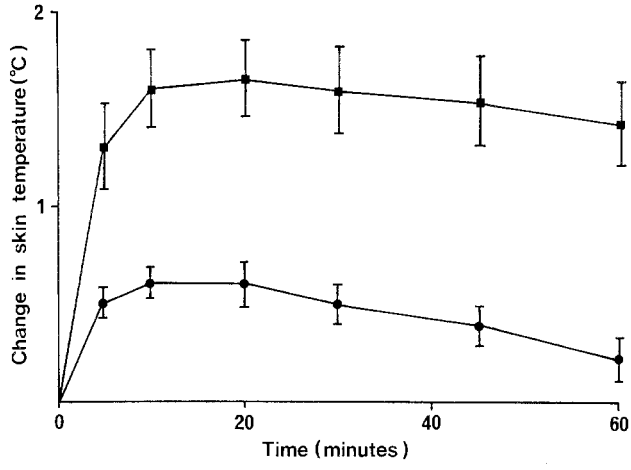

Fig. 3. Facial temperature after infusion of an enkephalin analogue DAMME in those positive (upper line) and negative (lower line) for CPAF. CPAF positive cases show a greater and longer rise of temperature. (Taken with kind permission from [24])

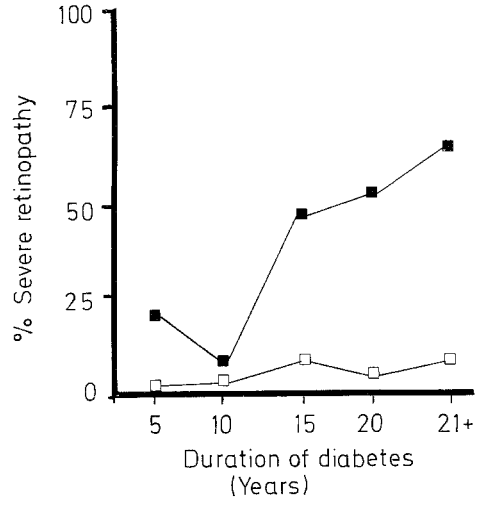

Fig. 4. The frequency of severe retinopathy (i. e. proliferative retinopathy or background retinopathy impairing sight) in CPAF positive and CPAF negative diabetics. Retinopathy is much commoner in CPAF negative cases and the difference becomes greater with increasing duration of diabetes. ■—■ CPAF −ve; □—□ CPAF +ve. (Taken with kind permission from [25])

one should continue to treat patients as well as possible.

There are clinical implications of these observations. Mason-type diabetics can be reassured that their risk of developing retinopathy is low. Furthermore, CPAF positive, non-insulin dependent diabetics probably require less close observation than CPAF negative cases and are much less likely to need treatment for progressive eye disease. In assessing the frequency of retinopathy and the effect upon it of treatment it will in future be necessary to take account of the CPAF status of the patients. If, for example, it were claimed that a particular regime had a beneficial effect it would be essential to make sure that the treated cases were comparable to the controls with respect of frequency of CPAF.

It is fortunate that the type of diabetes which we can predict by CPAF testing is mild both in the kind of treatment required and in the chances of developing serious complications.

We are talking here about the microvascular not the macrovascular complications of diabetes. We are now studying the frequency of coronary and peripheral arterial disease in CPAF positive and negative non-insulin dependent diabetics.

Those are my six propositions. They raise two questions, one concerning insulin dependent diabetes, the other non-insulin dependent diabetes.

1. What is the Non-Genetic Cause of Insulin Dependent Diabetes?

The discordant twin pairs ought to provide the ideal material for studying the aetiology of IDD since non-genetic causes must have operated in the affected twins and by studying them in comparison with their unaffected co-twins one should be able to identify these causes. The difficulty here is that in most cases we have not seen the pairs until some months or years after the diagnosis in the affected twin. Thus the evidence of the non-genetic cause might well have disappeared by the time we saw them. We have not been able to find any evidence of virus infection in the affected as compared with the unaffected twins nor have we been able to obtain any other indication of a possible environmental cause [11, 27].

The evidence for a virus cause of IDD in man comes from its seasonal incidence in young children [28] and the early finding of raised titres to Coxsackie B4 infection [29]. Recently an exceptional case of overwhelming virus infection leading to diabetes has shown that this can be a cause of IDD [30] but whether it is commonly so remains unproven.

We must conclude that environmental, i. e. non-genetic, factors exist which operate in genetically predisposed individuals to produce IDD but we do not know what these factors are.

2. Does Chlorpropamide-Alcohol Flushing Tell Us Anything About the Cause of Non-Insulin Dependent Diabetes?

The twin study has shown that non-insulin dependent diabetes is predominantly inherited. NIDD is strongly associated with chlorpropamide alcohol flushing [21]. CPAF is due to sensitivity to enkephalin [24]. Is this a chance finding or could enkephalin, and other peptides with opioid activity, play a part in the causation of NIDD?

There are two lines of evidence which suggest that they may.

Morphine Hyperglycaemia

It has been known for years that morphine, whose action is in many ways similar to that of opioid neuropeptides, when given in large doses causes hyperglycaemia [31, 32]; Claude Bernard himself was in no doubt that morphine could lead to hyperglycaemia [33]. More important are the observations of Borison [34] and Feldberg [32, 35, 36] that if morphine is injected into the ventricles or brain stem of cats there is a rapid and intense hyperglycaemia (Fig. 5 and 6) – and the same is true for B-endorphin [37], neurotensin [38] and bombesin [39]. The degree of hyperglycaemia varies greatly according to the precise site of injection of the morphine. The effect is reduced by general anaesthesia, section of the sympathetic or ablation of the adrenals. Feldberg concluded that the hyperglycaemia was due to a centrally innervated, sympathetically mediated effect.

Furthermore, opioids have a direct effect on insulin secretion. If morphine or B-endorphin are injected into the isolated pancreas insulin is released [40]. Dr. Irene Green, working in conjunction with us, has shown a similar effect of enkephalin on isolated islets. At low concentrations enkephalin stimulates the secretion of insulin by the islets but at higher concentration it has an inhibitory effect. It is clear therefore that neuropeptides are capable of raising blood glucose very considerably by a central effect on the brain stem and a peripheral effect on the pancreatic beta cells, and these effects, at least on the beta cells, may be dose reversible. The effects of neuropeptides on other tissues are also dose reversible. Thus at low doses the opiate antagonist naloxone causes analgesia, at high doses hyperalgesia [41].

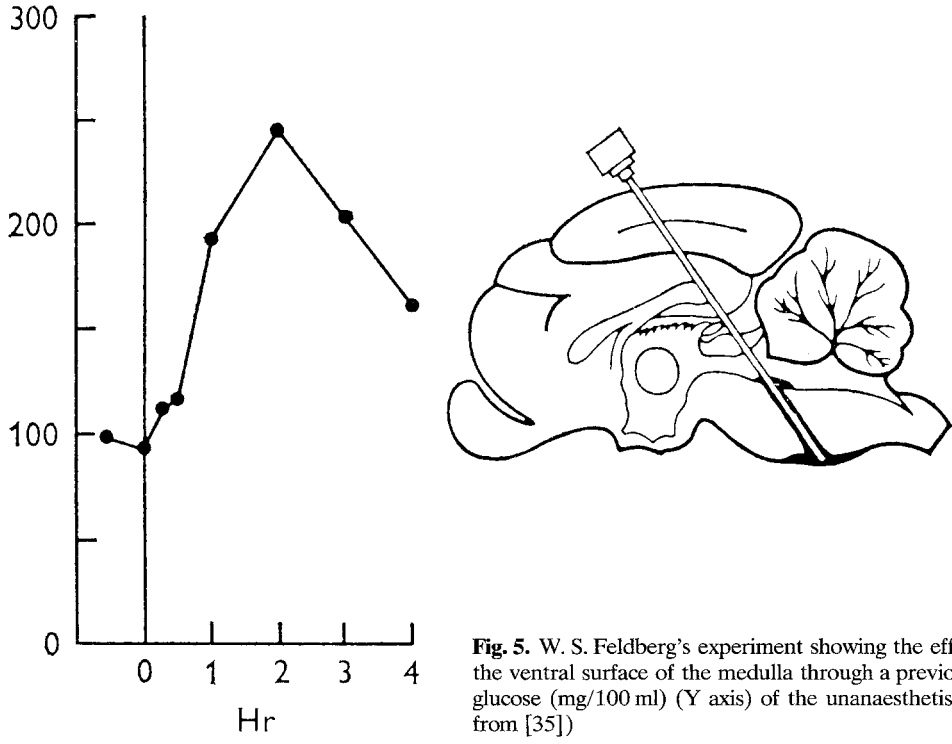

Fig. 5. W. S. Feldberg's experiment showing the effect of 0.75 mg morphine injected at the ventral surface of the medulla through a previously implanted cannula on the blood glucose (mg/100 ml) (Y axis) of the unanaesthetised cat. (Taken with kind permission from [35])

Enkephalin as a Neurotransmitter [42]

Enkephalin is found in the brain, and spinal cord [43, 44, 45, 46]. Its concentration is variable in different parts of the brain – it is high in the locus coeruleus, globus pallidus, periaqueductal grey matter and other brain stem structures. It is also found in profusion in sympathetic ganglia, splanchnic nerves and adrenal medulla [47] where its concentration is much reduced by section of the sympathetic trunk. Like other neuropeptides it is also found in the gut [48].

These observations are consistent with the view that enkephalin is a neurotransmitter concerned with sympathetically mediated effects.

We lack direct evidence of the role of enkephalin and other neuropeptides in the aetiology of non-insulin dependent diabetes. Since enkephalin is rapidly broken down in the blood its measurement has proved difficult. However, patients with NIDD may well have normal levels, their response to an enkephalin analogue infusion suggests they have a greater sensitivity to enkephalin and it may be this, rather than any greater or lesser level of enkephalin production, that is causally related to their diabetes.

Claude Bernard Reassessed

Scientific discoveries can have their negative as well as their positive aspects. The discovery of the pancreatic origin of diabetes and of the effect of pancreatic extract were of the utmost importance both in theoretical understanding and in clinical treatment. So long as diabetes was regarded as one disease these great discoveries were seen as conclusive; they solved the problem of what went wrong in diabetes – the islets failed – and how to treat it – give insulin. But diabetes is not one disease, and with the recognition

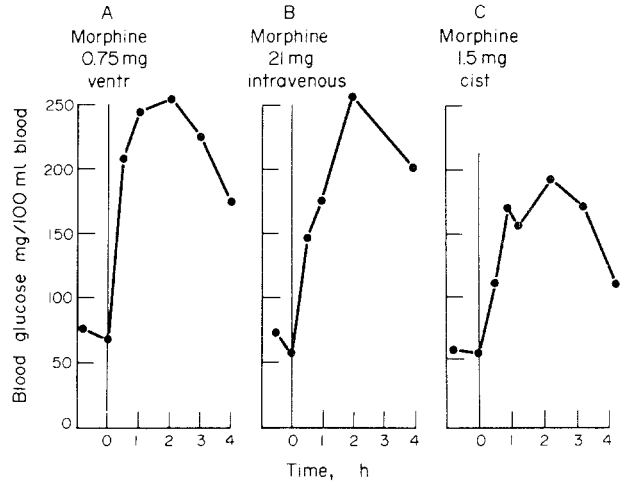

Fig. 6. Morphine causes a large and rapid rise of blood glucose when injected into the lateral ventricle (A), cisterna magna (C) or intravenously (B). (Taken with kind permission from [36])

of the fundamental distinction between its two types we are liberated from the constricting need to fit both disorders into a single pattern of causation.

Minkowski and Banting solved the essential problems of insulin dependent diabetes but they have unwittingly held up our understanding of the cause of non-insulin dependent diabetes by seeming to have solved that too. Thus Labhart in his Paracelsus lecture of 1977 said "Claude Bernard's hypothesis of angioneurotic diabetes was finally disproved by Minkowski's discovery" [49], and Joslin wrote that before Minkowski "the spell of Claude Bernard hung over the disease and confusion regarding its aetiology reigned" [50].

I take a different view. Claude Bernard made the greatest contribution to our understanding of non-insulin dependent diabetes which recent work is bringing into perspective. It was because others assumed that, since the pancreas was important in one type of diabetes it was in the other, his discoveries caused confusion. His observations were correct but his readers have for the last 90 years been conditioned to misinterpret them.

Piqûre

I return now to Claude Bernard's piqûre experiment – there it is but what does it mean? Everybody knows about it, and its clinical counterpart the temporary diabetes of subarachnoid haemorrhage and meningitis, but no-one knows how to fit it into any picture of the aetiology of diabetes. Bernard's biographer, the American physiologist Olmsted, said in 1938 "one certainly feels that the last word has not yet been said on the subject of the exact mechanism by which puncture of the floor of the fourth ventricle causes sugar to appear in the blood and urine" [51]. F. G. Young, writing over a century after the discovery of piqûre diabetes, asked "are we certain today that we know all about any nervous action on the secretion of sugar by the liver, and of insulin by the pancreas?", and went on "are the nervous stimuli from the floor of the fourth ventricle, or from the hypothalamus, involved in the development of any form of diabetes mellitus? The full significance of Bernard's experiments which led to the description of piqûre diabetes is not yet understood" [52].

Now perhaps we are beginning to understand how piqûre might fit in. Feldberg said "It is tempting to think that the site (of piqûre) is the same as that on which morphine and its derivatives act and that we imitate with morphine and its derivatives Claude Bernard's piqûre by a chemical or pharmacological lesion" [36]. To the "morphine and its derivatives" we may now add enkephalin and other neuropeptides. If this is correct then piqûre diabetes is a result of a temporary disturbance of enkephalin secretion.

This suggestion could easily be put to the test; is piqûre diabetes prevented by naloxone?

The Cause of Non-Insulin Dependent Diabetes: An Hypothesis

My suggestion is that as far as non-insulin dependent diabetes is concerned Claude Bernard was right; this condition is not the result of pancreatic islet failure but of a genetically determined alteration of sensitivity to endogenous neuropeptides acting via the sympathetic nervous system and adrenal medulla to affect hepatic glucose output and insulin release.

This suggested mechanism for the causation of non-insulin dependent diabetes may be wrong but it can be put to the test.

In case I seem to be claiming too much I close with the words of Claude Bernard "I do not claim to believe that we have yet reached a complete understanding of diabetes; we have on the contrary seen that we know less about it than we thought we knew" [53].

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