THE DIABETIC SYNDROME*

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Any model of the diabetic syndrome must be dynamic because the homeostatic processes which underlie the diabetic syndrome are themselves dynamic and the diabetic syndrome in this view is the pattern of derangements, some permanent, some reversible, which occur in the body when the homeostatic devices which are continuously attempting to return the levels of blood glucose and other associated metabolites such as ketones to basal values, are overstressed and fail partially or completely. One of the intriguing things about the homeostatic mechanisms controlling blood glucose levels, is the small reserve compared with other comparable biological mechanisms. This may be due to the fact that the genetic basis for the blood glucose homeostatic mechanism was determined during the time when man's diet was high in protein and low in carbohydrates, or at any rate, refined carbohydrates.

The two main components of the diabetic syndrome (Crombie 1964) are the biochemical or metabolic on the one hand and the pathological on the other.

*The biochemical component. This consists of the derangements of blood and tissue chemistry which accompany and follow the hyperglycaemia of glucose intolerance. These include glycosuria, ketosis and other associated biochemical abnormalities and the cardinal signs and symptoms directly related to these biochemical abnormalities, namely: polyuria; pruritus vulvae; balanitis; dry mouth; thirst; loss of weight; lassitude and loss of energy; transient disturbances of vision due to refractive changes; and constipation.

The pathological element. This term covers the specific ‘complications’ of the diabetic syndrome, including neuropathy, nephropathy, retinopathy, and possibly other (as yet unsuspected or ill-defined) changes in the tissues. Any or all of these conditions may accompany abnormal glucose tolerance, or they may be entirely absent.

The complications or components of the pathological element may

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reasonably be presumed to be secondary to diminished glucose tolerance or hyperglycaemia for the specific complications are never found without evidence of past or present diminished glucose tolerance and hyperglycaemia (Crombie 1964). The only factor common to all patients with the ‘diabetic syndrome’ is diminished glucose tolerance, and almost any combination of the other components can be found. Diminished tolerance—even a ‘florid’ one—can exist without evidence of the other components.

*Glucose tolerance.* In this model then, the biochemical abnormality always precedes the pathological and any factor which provokes hyperglycaemia is potentially diabetogenic (figure 1).

![Mechanism of glucose intolerance](image)

**Figure 1.**

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Any such factor or group of factors acting strongly enough and long enough will first press the insulin-producing reserve to the limit of its productivity, then exhaust that reserve and finally, by subsequent overstimulation, lead to destruction of part or all of the islet cell system which forms the basis at least for the insulin-producing mechanism (Ogilvie 1935, Edwards 1960, Beckett 1962). There are possibly other systems subsidiary to the insulin-producing mechanism which are called into action as part of the homeostatic control system of blood glucose and associated metabolites such as ketones and which have an insulin-like activity, but for the purpose of this description they are subsumed under the title ‘Insulin-producing mechanism’.

This mechanism of episodic and partial failure of the insulin-producing mechanism is certainly evident during the course of
established clinical diabetes. For example, a patient may be stabilized on a dose of say 20 units of insulin per day with peak blood glucose levels maintained below 180 mg per cent under all ordinary circumstances. If this patient develops a severe infection such as a pyelitis or pneumonitis, the insulin requirements usually rise quite steeply and if they are not supplied pro rata by an increase in the daily dose of insulin, the resultant high sustained blood sugar levels may lead, through overstimulation of the remaining insulin-producing mechanism, to further partial failure. If this happens, the insulin requirements of the same patient when the infection has subsided and the diabetes is once again stabilized, will be found to be greater than they were before the infection. The episodic type of clinical progress, by extrapolation or inference can be assumed to occur even before the onset of overt clinical diabetes. Clinical diabetes has been reached when the insulin-producing reserve has been reduced to such an extent that even on the patient's normal diet and under—for him—basal levels of diabetogenic activity, he is unable to reduce blood glucose levels below the renal threshold for a large part of the day. Prior to this, he or she may only have had episodic phases of relative failure during the peaks of activity of such diabetogenic factors as acute infections or pregnancy.

Factors influencing glucose tolerance

Excessive carbohydrate intake probably acts directly by increasing the load on the insulin-producing mechanism.

Physical destruction of the pancreas, caused by haemochromatosis, carcinoma or chronic pancreatitis, reduces the insulin producing reserve.

Hormones circulating in abnormal amounts (which may reduce glucose tolerance) include growth hormone in acromegaly, other anterior-pituitary hormones from pituitary tumours, thryoxine and glucogenic adrenocortical hormones. Stress, in the form of infection and severe emotional or physical strain, may be mediated through excessive amounts of hormones. Pregnancy, too, may exert its effect by temporarily raising the concentration of hormones in the blood.

Multiparity may reflect the cumulative effect of successive pregnancies; but the fact that multiparity increases a woman's chances of becoming diabetic but does not make the disease develop earlier in life is still unexplained.

Obesity exerts its effect partly through its relation to overeating but is probably also associated with certain insulin antagonists, (Lowy, Blanshard and Phear 1961, and Vallance-Owen 1962).

Ketones and free fatty acids. Even if the anti-insulin effects of free fatty acids (Randle et al. 1963) and ketones (Taylor 1963) are not the
primary or initiating causes of diabetic failure (Jenkins 1967) they
can certainly contribute to the final vicious circle of failure (Crombie
1964).

*Insulin antagonists* have been demonstrated in the blood of dia-
etics by Vallance-Owen, Hurlock and Please (1955) and Randle
(1963). The antagonist described by Vallance-Owen, Hurlock and
Please is associated with the albumin fraction of the plasma and
called by them a synalbumen antagonist; but the insulin so bound is
at least partly effective in fat tissues, and this selective effect leads
to a disproportionate rise in the fat deposits. Vallance-Owen has
proposed that patients who become diabetic are in hyperdynamic
equilibrium with regard to insulin and synalbumen antagonists from
birth. Vallance-Owen (1962) has shown that the synalbumen
antagonist described by him is probably inherited as an autosomal
dominant possessed by approximately 25 per cent of the normal
population. This means that it can be the primary cause of only a
small proportion of all ‘diabetes’. Vallance-Owen has further
suggested, however, that synalbumen antagonists must necessarily
be present before any of the other diabetogenic factors except those
resulting in physical destruction of the pancreas can produce a
phase of failure. In the model presented here, it is suggested that all
the diabetogenic factors previously described, including synalbumen
antagonists, whether they act continuously or intermittently, pro-
duce their final effect *via* this hyperdynamic balance with insulin.
There are probably other anti-insulin substances than those men-
tioned above.

*Genetic effects* may be the summation of the genetic content of
other factors, insulin antagonists in particular. But perhaps some
people inherit a greater insulin-producing reserve than others, or
an insulin-producing mechanism more resistant to some or all of
the factors which impair glucose tolerance.

The results of the survey by the College of General Practitioners
Working Party (1965) have shown that only diabetes mellitus with
onset before the age of 30 can have any strong genetic element in its
aetiology. The greater the age at onset the more important are
environmental factors relative to genetic factors in the aetiology.
This familial relationship with age was investigated by the college
working party and can be enumerated as follows. Patients whose
clinical diabetes began before the age of 30, have 26 times as many
diabetic brothers and sisters as normal people of the same age. The
ratio, called the ‘K’ or kinship value, for diabetics who become
clinically ill between 30 and 49 is 6, between 50 and 69 is 2.4, and
over 70 is 1.5. In other words, only diabetics with onset at an early
age can have any strong hereditary component in the aetiology of
their condition and for those whose onset is late in life, environmental
Ageing may act merely through accumulation of various diabetogenic factors or through a gradual attrition of the insulin-producing mechanism or of the complementary glycogenic mechanism of the liver. The oral glucose tolerance test (OGTT) shows a gradual rise in the one hour peak with age, but only after the age of 70 is there a rise in fasting values (College of General Practitioners Working Party 1962b). It was established in the same survey that one in six of all males over 50 and one in three of all females over 70 have 'diabetic' glucose tolerance but no one would suggest that anything but a small minority of these people have clinical diabetes. This diminution of tolerance with age raises one other characteristic of failing glucose tolerance, namely its differing tempo at different ages. Patients under 30 seldom linger for more than a week or two at most in the intermediate stage of failure and rapidly become frankly diabetic. With increasing age the pace is slower and many patients, particularly women over 70, may have a mild degree of abnormality which deteriorates so slowly that it has no apparent effect on life expectation. This difference in tempo and the slow deterioration of tolerance with increasing age may be due in part to an increasing insensitivity of the insulin-producing mechanism to stimulation by rises in blood sugar, rather than diminution of the actual insulin production reserve. Such a relative insensitivity would also be protective of the insulin-producing reserve. This insensitivity may in turn be related to some defect in the rate of exchange of metabolites across the capillary and islet-cell boundaries and reflect the other more general cardiovascular degenerative changes that are also known to be associated with age and diminished glucose tolerance.

The glucose-insulin dynamic balance. In the model of diabetes presented here, clinical diabetes is an end point, associated with islet-cell exhaustion or destruction through episodic and usually repeated overstimulation following exhaustion. The subsequent clinical picture will obviously depend on the factors which precipitated failure. For example, insulin antagonists will presumably continue to act and interfere with the action of insulin whether endogenous from the residual islet-cells or exogenous as insulin given by injection. On the other hand, where failure was due to primary degeneration in the insulin-producing mechanism, this will be more easily controlled by treatment. Where the activity of the antagonist fluctuates, the diabetes is 'brittle'. Occasionally, spontaneous remissions occur in early diabetes mellitus (O’Sullivan 1966) and are presumably due to the remission in the activity of an insulin antagonist or some other diabetogenic activity which provoked
the initial intolerance.

As we have seen, only a minority of individuals with glucose intolerance will enter the ‘malignant’ phase.

The biochemical component of the diabetic syndrome therefore is a dynamic process, with no sharp dividing line between normality and abnormality, other than divisions created arbitrarily by definition.

In contrast to the infinitely variable biochemical or metabolic component, where there is no sharp division between normality and abnormality of the hyperglycaemia of diminished glucose tolerance and the associated secondary effects: glycosuria, the cardinal symptoms and ketosis, are the all or none features of the ‘pathological’ component.

Neuropathy both of the autonomic and peripheral nervous systems can be present from the earliest phases of severe intolerance. Peripheral neuropathy can improve when the biochemical abnormality is brought under control, though it often takes many months. Autonomic nervous system neuropathy, as evidenced by postural hypotension, impotence and localized flushing, on the other hand once established is usually permanent. This is presumably related to the absence of the neurolemma sheath in the autonomic nervous system fibres.

Symptoms of peripheral neuropathy often follow the control of episodic worsening of the clinical condition.

The other pathological complications, retinopathy and nephropathy, usually manifest themselves first 15–20 years after the first episode of relative biochemical failure and, once initiated, progress inexorably, almost uninfluenced by metabolic control, either spontaneous or following treatment. This in turn suggests that nephropathy and retinopathy are the result of some irreversible or near-irreversible process which needs only to be triggered off. The rest of this paper is concerned with the hypothesis that autonomic nervous system neuropathy is the link in the chain between the biochemical component on the one hand and the specific complications or pathological element on the other.

The basic lesion of the pathological component is diabetic microangiopathy. So far as we can tell at present, the morphology and natural history of diabetic micro-angiopathy is similar in all tissues in which it occurs. These include, as well as the retinæ and kidneys, the skin, muscles, peripheral nerves, the walls of larger vessels, the intestines, nail beds and conjunctivæ (Fagerberg 1966).

The changes in the retinæ, which probably typify changes elsewhere occur in the following sequence:

(a) venous dilatation;
(b) localized areas of capillary dilatation with the classical micro-aneurysms;
(c) localized exudates;
(d) obliteration of the capillary beds in these localized areas;
(e) revascularization by arcades of thin-walled fragile capillaries and
(f) haemorrhages from these fragile new vessels as the origin of retinitis proliferans.

In the retina the time interval between the first manifestation of severe biochemical abnormality and stage (a) of micro-angiopathy seems to be about 5–15 years. The interval between venous dilatation (stage (a)) and capillary dilatation with micro-aneurysm formation (stage (b)) is much shorter, possibly in the range 2–5 years. The formation of localized exudates and subsequent local obliteration of the capillary bed takes a similar length of time. Although venous dilatation is a generalized phenomenon, micro-angiopathy is typically patchy. Different localized patches may be at different stages of development and provided that only a few scattered areas are affected, ‘healing’ can apparently take place in that revascularization and subsequent retinitis proliferans (stages (e) and (f)) do not follow stage (d) unless a confluent area of capillary obliteration of a size sufficient to cause the degree of anoxia in the retinal tissue necessary to stimulate stages (e) and (f) also occurs.

In the model presented here, it is suggested that each phase of episodic relative biochemical failure may cause patchy autonomic nervous system neuropathy. This is followed by the development of micro-angiopathy over a period of 15–20 years in the local capillary beds supplied by each of the affected autonomic nerves.

At a very early stage, at least by (b) above, there is evidence of endothelial and basement membrane thickening in the smallest capillaries with an increase in the thickness of the smooth-muscle layers of the arterioles and arteriovenous shunts. However it has been established that none of these changes are evident at the onset of acute diabetes in young people. In these same young diabetics evidence of any clinical manifestation of the pathological element is rare before puberty but so also is evidence of peripheral neuropathy.

Diabetic peripheral neuritis affects nerves already subject to other factors reducing their vitality (Gilliatt 1966). For example in women aged 50–60 the brachial plexus and median nerve in particular are commonly affected as is the sciatic nerve at all ages.

Neuropathy can occur at the earliest stages of clinical diabetes and usually precedes the other complications. Peripheral neuropathy usually first appears immediately after a phase of poor control or episodic biochemical failure and its effects are reversible if the biochemical abnormality is well controlled. On the other hand when autonomic nervous system neuropathy occurs, its effects (impotence, diarrhoea, postural hypotension, local flushing) tend to be permanent.

It is the long time interval of 15–20 years, between the episode of
biochemical failure which initiates a leash of local areas of micro-angiopathy and the clinical manifestations of that micro-angiopathy which apparently weakens the effect of good biochemical control on the development of micro-angiopathy since the benefits of such good control will only be evident some 15–20 years later and will have little or no influence on lesions already initiated.

The description given above applies to the retina but a similar development has been demonstrated in skin and by inference probably occurs in all tissues in the body in which micro-angiopathy also occurs.

If autonomic neuropathy is the link, then this could act by releasing the normal control of the arteriolar input, venule output and the arteriovenous shunt in the capillary bed supplied by the particular nerve fibre. The primary lesion in all the pathological complications would then be the result of the simple effect of permanently closed arteriovenous shunts with direct and sustained arterial pressures transmitted directly to the venous side of the capillary beds with effects which are visually obvious in the retinae. Sympathectomy for example leads first to a general increase in peripheral blood flow due mainly to the initial opening of all arteriovenous shunts. This is followed in two to three weeks by a great diminution in this flow but usually not to presympathectomy levels. The mechanism of this is not fully understood but may be related, as in early stages of diabetic micro-angiopathy, to the overgrowth of smooth muscle in the arterioles, venules and arteriovenous shunts. In other words, the control of blood flow is now based on the primitive direct response of smooth muscle to local changes in metabolites and blood pressure. After sympathectomy, the main effect of this smooth-muscle overgrowth is to close off the arteriovenous shunts but to still allow an increased blood flow through the capillary beds. In diabetic micro-angiopathy the dynamic balance between smooth-muscle overgrowth in the arterioles, venules and shunts is such that the latter are closed permanently, and the arterioles allow blood into the capillary beds where the increased resistance in the venules leads in turn to stagnation and stasis of blood flow through the now dilated capillary bed which is devoid of smooth muscle. The basement membrane thickening and endothelial cell overgrowth in the capillaries which accompany the earliest evidence of dilation would then be a direct response to increased capillary bed pressure and relative anoxia accompanying stasis. It would be surprising if the effects of diabetic neuropathy coincided exactly with those of surgical sympathectomy and the analogy cannot be pressed too far.

Confirmation of this hypothesis by direct observation of a reduction in the autonomic nerve fibres to an affected eye or kidney commensurate with the degree of micro-angiopathy clinically evident
Summary

The diabetic syndrome consists of a ‘metabolic’ element and a ‘pathological’ element. The ‘metabolic’ element consists of diminished glucose tolerance and its secondary effects, hyperglycaemia, ketosis and glycosuria with the associated cardinal symptoms of polyuria, pruritis vulva or balanitis, dry mouth, thirst, constipation, loss of weight and energy, and transient disturbances of vision due to refractive changes. The ‘pathological’ element includes neuropathy, nephropathy, retinopathy and possibly other as yet undefined abnormalities.

Glucose intolerance (and hence also the secondary effects which constitute the ‘metabolic’ element) is an infinitely variable characteristic in the general population (compare hypertension) and there is, therefore, no firm boundary line between normality and abnormality. Also it is reversible by treatment and almost certainly has a multiple aetiology and no one cause.

The ‘pathological’ element in contrast, once initiated progresses inexorably. There is therefore a clear cut boundary between normality and abnormality.

It is suggested that the complications may be initiated by some abnormal metabolite associated with diabetic ketosis which need not continue to act once it has triggered off the ‘pathological’ element.

Finally, it is possible that ‘autonomic nervous system neuropathy’ is the fundamental ‘complication’, the link between abnormal metabolites and the specific complications, and that the other changes are secondary to this.

REFERENCES