Modern Views on Glycosuria

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Perhaps the most striking impression one has on looking back over the past twenty years of Medicine, is, oddly enough, not one of advance, but of the number of times we have been proved wrong in our most cherished of dogmas.

The practitioner of Medicine has, of course, to dogmatise; his treatment depends on his dogma, and his practice on his treatment. He has to be "scientific" if he would be "well informed"—that is to say—he would like to think that any view he holds or treatment he orders is well founded upon the rock of sound scientific experiment.

Alas for our peace of mind, in Medicine there is no standing still or digging in; only too often in the voice of Smuts, we must strike our tents and move on.

The time at my disposal limits me to only one aspect of glycosuria and that its most important, namely, its cause, I shall exclude so called alimentary glycosuria, arising from excessive intake of carbohydrate, and the glycosuria associated with low renal threshold. Properly, these do not fall under the heading of abnormality or disease, although there are workers who regard both these conditions as very early stages of diabetes.

I wish to show how the ordinary Medical School teaching of eighteen years ago has had to be changed, and to plead on behalf of the patient who insists that your treatment is doing him no good. If much that I imply sounds like heresy—well, Medical men are renowned for their stubbornness and obstinacy when the time comes that a cherished position be abandoned.

Let me give you briefly the history of my own attitude to diabetes mellitus—originally obtained some twenty years ago from teachers and text-books, and still obtaining in text-books and monographs of the present day. I assume that by diabetes mellitus we mean pathological hyperglycaemia with or without glycosuria.

We were taught that all glycosuria is diabetic, unless shown to be due to excessive intake or lowered renal threshold, and that all diabetes is due to a deficiency of the pancreas. We held that the high blood sugar is mainly responsible for the train of symptoms associated with diabetic ill-health; we implied that sugar in excess in the blood and tissues acts as poison to the organism.

The following extracts from standard works exemplify the prevalence of this teaching:—

Tidy [1934] defines diabetes mellitus as follows: "A condition due to deficiency of the internal secretion of the pancreas producing chronic abnormality of the carbohydrate metabolism, and characterised pathologically by hyperglycaemia and by long continued glycosuria and clinically by thirst, polyuria, emaciation and tendency to coma."

Duncan [1935] states: "Diabetes mellitus is a disease of metabolism characterised by a deficiency of the internal secretion of the islands of Langerhaus of the pancreas, insulin."

We taught, and were taught, that the main object of treatment is to reduce the blood sugar to normal levels and that no treatment is efficient unless this end is achieved. As Joslin says: "Urinary sugar is the red lamp of danger, and a blue Benedict or Fehling spells safety." A high blood sugar we were repeatedly informed imposes a strain on an already overwrought pancreas, and hastens the degeneration of this hardly beset organ.

Extracts indicating this attitude towards a high blood sugar are quoted as follows:—

Osler and McCrae [1930a] states as regards treatment: "the endeavour is to keep the urine sugar free, the blood sugar as near normal as possible and the patient in the best general condition." Duncan [1935b] states: "the object of treatment is always the same, that is, restoration of normal metabolism. By this is inferred the maintenance of a normal blood sugar and freedom from glycosuria." Joslin [1935a] says: "the urine is to be made sugar free and the blood sugar normal—

(1) because normal values are obviously the best;
(2) because normal high blood sugar is a stimulus for insulin secretion and the impaired island tissue should be spared overwork,
(3) because the removal of the glycosuria proves utilisation of the diet . . . .

Price [1934] states: "The principles which govern treatment are:—

(1) The blood sugar of the patient when fasting should be within the normal limits.
of 0.08 per cent. and 0.12 per cent., and should not rise above 0.19 per cent. at any time of the day. It follows from this that the urine should never contain any sugar.

Duncan [1935c] says: "with effective treatment the arterial changes are largely checked; the retinitis is halted and moderate improvement is the rule. These desirable results have not been obtained, in my experience at least, unless a normal blood sugar is maintained. Mild degrees of hyperglycaemia doubtless contribute to the progressiveness of degenerative changes."

Osler and McCrae [1930b] states: "The excess of sugar renders the body a favourable culture medium for pus organisms."

Duncan [1935d]... "Degenerative changes, due to a chronic high blood sugar, have been gradually developing. The arteries may be thickened causing gangrene. The heart may be affected, and failing vision be a prominent symptom."

These views formed the corner stone of our faith, and on them was founded the rationale of our treatment. I shall hereafter refer to them as the Creed. We gave minimal amounts of carbohydrate, moderate amounts of protein, enormous amounts of fat. Foods were meticulously weighed. Our results were interesting. Broadly speaking, young diabetics lived miserably and died speedily, old and especially obese subjects improved dramatically in many ways, and as the incidence of diabetes was higher in the old than in the young, the sum total of our results seemed good, and our creed was justified. Diabetics of all ages, however, if wasting rapidly, died within a brief period, unless some severe septic focus could be found and evacuated. We looked forward eagerly to the discovery or invention of the responsible pancreatic hormone, and in due course some fifteen years ago "Insulin" arrived.

True to our creed we welcomed insulin and foresaw a marvellous new era for the diabetic.

The next five years—some would say fifteen—were the most tantalising both to the diabetic and the doctor that one could conceive. Our first disappointment arose from the fact that the effect of insulin was apparently a most variable affair. In some the drop in blood sugar was excessive, in others there was hardly any fall, in all the effect was shortlived, and to keep the blood sugar down to ideal levels, many injections per day were required. Indeed, in order to achieve our ideal, we were forced to combine diet with insulin, and the end results seemed to be simply that we had added a syringe to our scales. Acute diabetics drifting to coma were, however, dramatically reduced, and it was clear a new era had indeed set in.

Roughly this was the point one had reached in 1930. By struggling with diet and insulin I tried to keep the urine sugar free and the blood sugar level down to normal. The daily allowance of carbohydrate was still strictly limited. While many diabetics—particularly the elderly, seemed happy and contented on this regime, the younger subjects led a life far from ideal. Insulin reactions were common, and the mental agony induced by the appearance of sugar very real. Many developed amoral habits of lying and thieving, their craving for sweet things not infrequently proving overwhelming.

I am reminded here of a young woman who had been in and out of hospital for a year because of left abdominal pain which came on at night whenever her diabetes was "properly" controlled. On 30 units of Insulin a day, and a low carbohydrate diet, she remained sugar free, but developed nocturnal pain. She craved sweets and ices, and lied when she had sinned, but her urinary sugar always gave her away. She insisted Insulin made her ill, and the war between her feelings about Insulin and my faith in my creed was rapidly becoming critical.

About this time a young medical diabetic was visiting Europe, and wrote Dr. R. L. Girdwood a long letter of his experiences. He found that diabetics in England were receiving about 50 grammes of carbohydrate per day while at reputable clinics in certain continental cities 120 grammes and even 200 grammes per day were allowed. The statement of my patient that treatment made her worse, had shaken my belief in the creed somewhat rudely, and the fact that experts were giving from 50 to 200 grammes of glucose shook it still further, so I decided to make an experiment. I agreed to let her eat whatever she wished, provided she in her turn expected the worst. To my surprise from that day she became a normal woman, put on weight, lost her nocturnal abdominal pain, and returned to her duties as a teacher. Most amazing of all her Insulin requirement remained unchanged for a while and then had to be reduced. For years her health remained good on normal full diet, and so far as I know she is well and working today on 35 units a day.

This experience was repeated many times during the ensuing year or two, so I was forced to abandon my creed, strike my tents and march. Being in the wilderness without a creed, I decided to treat each case on its merits, and if the patient improved the treatment was regarded as right.
"NOT INFREQUENTLY"
At this stage I divided diabetics into two groups:—

**Group A.** Losing weight rapidly and showing Ketone bodies in the urine. These were given insulin and allowed a liberal diet with restriction of fat only. The insulin was adjusted to exclude acetone but reduced if sugar also disappeared. No blood sugar estimations are made.

**Group B.** No marked loss of weight. No acetone. These were given an itemized diet—no weighing of food—and approximately 100 grammes each of carbohydrate protein and fat per day.

This method of treatment gave good results, the patients lost their fear of sugar, and there never was any difficulty in deciding when to give Insulin and when to withhold it.

Of course, I regarded myself guilty of heresy—but so far as I could judge clinically the end seemed to justify the means.

From this time onward my faith in the creed became more and more shaken. Let me put before you some of the difficulties that kept obtruding themselves.

1. Why had Insulin such a bad reputation in the lay mind? One constantly met with opposition to its use, or the statement that so and so had it and it only made him worse.
2. Why did elderly diabetics so often insist that even small doses made them feel ill, especially when there was evidence of coronary disease?
3. What evidence was there that sugar was in itself harmful? When one studied the mode of death in diabetics, it seemed they died either in coma with Ketosis—a disorder of fat metabolism, or of some atheromatous accident due to fatty changes in the vessels. Indeed, both these conditions seemed more nearly related to fat than to sugar, so why not incriminate fat?
4. Why were clinicians beginning to report cases where up to 2,000 units of potent Insulin in 24 hours had no more effect than injections of water. Case 6247 reported by Root [1929] is an example.
5. Why did we speak of peripheral gangrene accompanied by glycosuria as diabetic gangrene, when in fact the gangrene in these cases differed in no respect from ordinary arterio-sclerotic gangrene. Muir [1936] states “in a limb the gangrene must frequently met with is of the senile type and is caused by arterial thrombosis resulting from advanced atheroma or calcification of the media. In diabetes, gangrene is not uncommon, and is due to similar changes, these tending to be marked in this disease.”

The following table, Joslin [1937a] shows how gangrene in diabetes with few exceptions occurs in the arterio-sclerotic age periods:—

**GANGRENE IN RELATION TO AGE AT ONSET OF DIABETES.**

<table>
<thead>
<tr>
<th>Age at onset of diabetes</th>
<th>1898-20</th>
<th>1923-27</th>
<th>1928-35</th>
<th>Total</th>
<th>Per Cent.</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 - 30 ...</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>7</td>
<td>1.7</td>
</tr>
<tr>
<td>30 - 50 ...</td>
<td>26</td>
<td>26</td>
<td>66</td>
<td>118</td>
<td>28.4</td>
</tr>
<tr>
<td>50 - 60 ...</td>
<td>23</td>
<td>29</td>
<td>98</td>
<td>150</td>
<td>36.4</td>
</tr>
<tr>
<td>60 - 70 ...</td>
<td>23</td>
<td>22</td>
<td>67</td>
<td>112</td>
<td>27.2</td>
</tr>
<tr>
<td>70 - 80 ...</td>
<td>8</td>
<td>4</td>
<td>13</td>
<td>25</td>
<td>6.2</td>
</tr>
<tr>
<td>Total</td>
<td>84</td>
<td>82</td>
<td>246</td>
<td>412</td>
<td></td>
</tr>
</tbody>
</table>

6. Why did this type of gangrene practically never occur in young diabetics if the diabetes was responsible?
7. Why did our very definitions of diabetes and hyperglycaemia differ from book to book and writer to writer?
8. Why did no two experts agree either upon diet or Insulin dosage in any given case, diet varying from 100 to 300 grammes of glucose per day?
9. Why, if it is necessary to rest the diseased pancreas by giving a low carbohydrate diet, should a liberal carbohydrate diet often if not invariably lead to compulsory reduction in the insulin dosage (Himsworth [1934a]). Surely it should be the other way about, especially when we think of the statement so often made, that each unit of Insulin can only deal with so many grammes of sugar? (Joslin [1937b]).
10. Why did Himsworth find that a low carbohydrate diet for seven days caused a *fall* in glucose tolerance, whereas a high carbohydrate diet actually raised it? (Himsworth [1934b]).
11. Why does it sometimes occur that no demonstrable macroscopic or microscopic lesion can be detected in the pancreas in cases dying of diabetes mellitus? (MacCallum [1937a]).
12. Why should a person dying of diabetes mellitus show an abundance of insulin in his pancreas? (Baker, Dickens, Dodds [1924a]).

The more that thoughts of this kind came crowding in, the more was one forced to ask—is there not possibly something wrong with our
creed that a high blood sugar is always bad, that the aim and object of all our endeavours must be a reduction of the blood sugar to normal levels?

In our concentration on the blood sugar have we not lost sight of wider aspects; are there not many diseases with a common factor—namely hyperglycaemia? Is it not possible that a high blood sugar may exist in the presence of a normal pancreas and an abundance of Insulin?

I will assume, gentlemen, that my heresies have loosened your tent ropes and that you are almost prepared to march.

Let me now give you some of the results of recent experiment and I feel you must abandon the comfortable resting-place you have occupied so many years.

1. It is a classical experiment that if you remove the pancreas of the dog, the animal develops diabetes and dies in ketosis and coma. (Minkowski and Von Mering [1889]).

But it is somewhat of a shock to hear that the removal of the pancreas of the pig does him surprisingly little harm. It is only when you then inject anterior pituitary hormone that he develops severe diabetes and ketosis. And who is to say which animal man most nearly approximates, the pig or the dog? (Lukens [1937]).

2. If we inject anterior pituitary hormone into a dog, the animal eventually develops permanent diabetes mellitus very like that of the depancreatised animal, but the pituitary diabetic dog can live without insulin—the depancreatised animal cannot. (Young [1937]).

3. And if you take away from a dog both pancreas and pituitary then he no longer develops ketosis and coma. (Houssay and Biasotti [1931]).

4. There is much human and other evidence to show that diabetes can and does exist without a demonstrable lesion of the pancreas or insufficiency of insulin. (MacCallum [1937a], Baker, Dickens and Dodds [1924a]).

So you see we are being forced away from the view that hyperglycaemia and hypoinsulinism are always as directly related as our text-books would have us believe.

Indeed a new problem has arisen in Medicine, namely, when is a case of diabetes due to hypoinsulinism? What are the facts? If we collect all the cases we have encountered who have glycosuria and a high blood sugar, i.e., diabetes, we could fairly put them into one or other of the following groups (after Oliver [1937]):—

II. Any disturbance of endocrine function may be accompanied by diabetes, e.g., acromegaly, hyperthyroidism, suprarenal tumour, etc. Here the injection of insulin has usually little effect.

II. Intracranial upsets, whether due to trauma, operation, apoplexy, neoplasm, encephalitis. Here, also the response to insulin is poor.

III. Arteriosclerosis and coronary thrombosis. Here insulin is not well tolerated.

IV. Disease of the liver, e.g., catarrhal jaundice, cirrhosis, pernicious anaemia, cholecystitis, gout, haemochromatisis. Here the insulin requirement is variable, sometimes temporary, and usually diabetic restriction suffices.

In these four groups the pancreas presumably is able to supply its full quota of insulin, but the high blood sugar and glycosuria are due either to the antagonistic effects of anterior pituitary hormone, adrenalin and thyroxin, or to the inability of the liver to store sugar as glycogen or to the inability of the tissues to use sugar in the presence of adequate supplies of insulin.

V. In this group fall the so-called acute diabetics, characterised by rapid loss of weight, marked acetonuria, increasing weakness and polyuria and speedy death, unless large doses of insulin and glucose are immediately available.

The striking and rapid improvement produced by insulin in this group clearly distinguishes it from the other four. The dosage tolerated is so much higher and the benefit so much more dramatic, that there is little doubt this type of diabetes is in large part due to hypoinsulinism. Nor dare we withhold glucose. Indeed, in the very severe cases approaching or actually in coma, we pay little heed to lowering the blood sugar, the need is for plenty of sugar and plenty of insulin.
So impressed have I been by the striking difference between acetone free and acetone producing diabetics that I feel sure that one of the first principles upon which our New Creed is to be based is the presence or absence of acetone.

What, then, is the meaning of acetone? Many are the workers and their views on this subject. Summed up it would seem that:

1. If the liver is absent, ketosis hardly occurs. (Chaikoff and Soskin [1928], Jowett and Quastel [1935]).

2. If the liver glycogen is low, then ketone bodies are formed. (Major and Mann [1932], Murlin, Nasset, Murlin, Manly [1936]).

3. In depancreatised diabetic dogs the administration of glucose by mouth removes ketosis when it is given in amounts adequate for glycogen retention in the liver. (Clark and Murlin [1936], Chaikoff and Weber [1927]).

In other words, ketone body formation is an index that (1) the liver has an insufficient supply of glucose (e.g., in starvation), or (2) though glucose is available the liver cannot use it for lack of insulin (e.g., hypoinsulinism), or (3) though insulin is sufficient it is not available owing to the antagonistic action of anterior pituitary hormone, adrenalin or thyroxin.

In any event, if there is ketosis, then the liver is low in glycogen and needs every assistance we can give it in the storing of glycogen, namely, glucose in plenty, and insulin in sufficiency.

We might almost go so far as to say that if there is an increasing lack of insulin then sooner or later acetone bodies will appear and will only recede on the injection of insulin.

Where, then have we arrived to-day? Unquestionably far from the position and the creed outlined at the beginning of this paper. How can it be otherwise when we think of the depancreatised dog dying in coma, and the defiant pig surprisingly little the worse for the removal of his pancreas; of the elderly diabetic who feels definitely worse though his blood sugar is lowered to normal; indeed, he may even go into hypoglycaemic coma, though his blood sugar is still three times the normal; of the insulin resistant diabetic in whom 2,000 units of insulin per day has no measurable effect; of the variation from expert to expert on the matter of diet—some giving 50 grammes of glucose and others 300; of the fact that there is little if any evidence that a high blood sugar does any harm at all, but much evidence that a high blood fat can destroy 8 (Allen [1917], Bourne [1937]); of the fact that some of us no longer order scales, and that our diabetics take insulin because they feel it helps them, and not because they are ordered to; of the recent discovery that the insulin requirement actually falls on the giving of a high salt diet (Sandstead [1936], Wilbur, Wilbur [1937]).

We have been forced to strike our tents and march, for the horizons of our knowledge are widening as endocrinologists daily offer new facts for our consideration. Once more we find ourselves driven back to clinical observation in our pursuit of truth, and are reminded that faulty interpretation of laboratory findings may lead us to creeds that are soon only to be abandoned.

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