London, the photomicrographs of our patient, a chef aged 66, was on account of nocturnal diarrhoea with incontinence of urine and faeces, for two years. On enquiry he had had good health until diabetes was discovered in 1936; since then control with diet and insulin had only been approximate. For four to five years his legs had been swollen; for three to four years he had had leg paraesthesiae, especially at night, with unsteady gait; and for two years, failing vision. He had had no dyspnoea.

On examination his nutrition was fair (weight 8 stone 2 lbs.) and there was moderate oedema below the knees only. There were no abnormal findings in the chest or abdomen, except that the liver was palpable at one finger’s breadth. His blood pressure was 115/70 and no jugular venous pulse visible. His pupils were irregular, mediumsized, reacting to accommodation, but only sluggishly to light. The fundus oculi showed hard macular exudates on both sides. The knee jerks were diminished, the ankle jerks absent, the plantar response flexor, below the knee the muscles were weak and wasted, and he had a stocking anaesthesia for pain, temperature, vibration and posture. His gait was ataxic. His urine showed albumin and sugar.

His W.R. was negative and the C.S.F. normal (protein 40 mgs. per cent.). His glucose tolerance test showed 278 (fasting), 434 (1 hour), 326 (1½ hours), 401 (2 hours), 393 (2½ hours), 376 (3 hours). He showed normal insulin sensitivity by a glucose insulin tolerance test. His blood urea was 31 mgs. per cent., plasma protein 7.2 mgs. per cent. (Alb. 3.6, Glob. 3.6), plasma cholesterol 207 mgs. per cent. His chest X-ray was normal; his barium meal and enema were normal, a three day fat balance showed 92 per cent. absorption, and there were no pathogens in the stools.

Despite truculence and food fads, and after a few hypoglycaemic attacks, fair control of his diabetes was established with P.Z.I. 60 units and S.I. 10 units. He obtained no benefit from vitamins. On discharge he had gained 22 lbs. in weight, and all his disabilities, except poor vision and leg oedema, were diminished but not gone.

Subsequently there were several admissions for hypoglycaemic coma and acidosis, for respiratory infections and heart failure which appeared later; his neurological signs showed only partial improvement and his diabetic control remained irregular.

Readmission (December 1948 to April 1949) in diabetic precoma (no insulin for 3 days).

Diabetic control was regained with difficulty. His urinary infections required three courses of penicillin and sulphonamide to clear it up (in December, January and March). During April testosterone injections were given. His albuminuria was little altered by these treatments; in January 3.9, 3.3, 2.4; in February 2.0, 0.9; in March 5.6, 4.7, 3.2, 5.2; in April 2.8, 2.9, 1.5 (gm. per 24 hours). He was now mildly anaemic (haemoglobin 8 gs. per cent.), his urea clearance (March 1949) was 100 per cent., his urinary 17-ketosteroids were 2.7 (in February) and 4.1 (in March) mgs. per cent. His blood pressure was now 160/90 and his electrocardiogram showed left ventricular stress (ST depression and evidence of horizontal heart). However, just before discharge, it was noted that he climbed upstairs to the third floor without dyspnoea, though this raised his jugular venous pressure from + 2 cms. to + 4 cms.

Readmission in October to December, 1950, with chest infection.
Since the last admission effort dyspnoea with orthopnoea and nocturnal attacks had appeared and he had just recently developed "bronchitis". He still had rare bouts of diarrhoea and paraesthesiae; his gait was nearly, but not quite, normal; his vision had deteriorated.

On examination, his weight was 9 stone, senile purpura was visible on his arms and he still showed ankle oedema. His peripheral arteries were palpably thickened, and his heart enlarged to clinical examination. The blood pressure was 150/85 and the jugular venous pressure was +2 cms. There were in the lungs generalised ronchi and signs of partial collapse in the right lower lobe. His fundus oculi showed haemorrhages, microaneurysms, thickened arteries and more exudates. His other neurological features were as on the previous admissions. His blood urea was 91 mgs. per cent., his plasma proteins 6.5 mgs. per cent. (Alb. 3.8, Glob. 2.7), and specific renal functions as follows: Effective renal plasma flow 194 and 176, glomerular filtration rate 56 and 65, filtration fraction 34 per cent. On fasting for 24 hours his urinary glycosuria did not fall but tended to increase; fasting glycosuria (urinary volume) 6-hourly=9.8 g. (0.39 litres), 12.8 g. (0.41 l.), 22.6 g. (0.72 l.), 16.7 g. (1.70 l.). This was evidence against a steroid type of diabetes. His urinary ketosteroids were little altered from 1949 (4.6 and 5.7 mgms. per 24 hours). A 450 mgm. testosterone implant was made in November.

Readmission December 1950 to January 1951, with basal bronchopneumonia. Urine culture sterile.

Readmission May 1951 to August 1951, with persisting and increasing cough and sputum, effort dyspnoea (now after 3 steps), and nocturnal dyspnoea.

On examination, oedema was generalised, including arms and legs. The jugular venous pressure was raised to 1 c.m. and the heart showed a triple rhythm. At both lung bases there were crepitations and air entry was poor. The blood pressure was 145/80, the blood urea 160 mgs. per cent., the urine was again infected and still grossly albuminuric. The vision and the fundi were further deteriorated (right 6/60, left 6/60). After treatment with antibiotics and for heart failure, he was discharged ambulatory, with leg oedema.

Readmission September 1951 to his death on November 27, 1951, on account of increasing weakness and hypotension. The findings on examination were little altered from those of the previous admission and again treatment of the urinary infection and of the heart failure restored him to ambulatory status with minimal ankle oedema, until he collapsed suddenly in the bathroom.

Note.—1. Six periods of antibiotic treatment for urinary infection, proved by culture before each course:—December, 1948; January, 1949; March, 1949; October, 1950; December, 1950; November, 1951.

2. The decreasing insulin requirement, indexed by the insulin dosage on discharge after each admission:—

<table>
<thead>
<tr>
<th>Date</th>
<th>Insulin Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>May, 1948</td>
<td>PZI 60 SI 10 (total = 70)</td>
</tr>
<tr>
<td>April, 1949</td>
<td>&quot; 40 &quot; 12 ( &quot; = 52)</td>
</tr>
<tr>
<td>December, 1950</td>
<td>&quot; 32 &quot; 26 ( &quot; = 52)</td>
</tr>
<tr>
<td>January, 1951</td>
<td>&quot; 20 &quot; 24 ( &quot; = 44)</td>
</tr>
<tr>
<td>November, 1951</td>
<td>&quot; 10 &quot; 10 ( &quot; = 20)</td>
</tr>
</tbody>
</table>

Diagnosis

? coronary infarction.
Coronary ischaemia and old hypertension.
Diabetes mellitus, with Kimmelstiel-Wilson nephritis and partially remitted diabetic neuritis (pseudotubes).

Autopsy Findings (Dr. Bernard Lennox)

At postmortem the body showed marked wasting and a little dependent ankle oedema as its only external features.

The heart weighed 450 g., and there was moderate left ventricular hypertrophy (20 mm.). There was an old infarct scar occupying a large part of the posterior wall of the left ventricle, but no recognizable recent infarct. In the coronary arteries there was very severe and extensive intimal thickening (mainly fibrous, with little yellow atheroma or calcification). The lumen of the right and of the left circumflex coronaries was reduced to a hair line, and the left descending to half its normal diameter. No recent thrombus was found but the degree of coronary obstruction is sufficient to account for sudden death. The heart valves were normal.

Vessels. The aorta showed severe atherosclerosis. Its major branches showed similar changes without obstruction; the limb vessels were not studied. The distribution of atheroma was rather curious: there were thick bright yellow patches of atheroma in many medium-sized hepatic arteries, and in one major division of one renal artery, but nowhere else. Hyaline thickening was well marked in the vessels of the kidney and the sciatic nerve, but the arteries and arterioles of the pancreas were remarkably healthy.

Pancreas. Grossly normal. The islets appeared to be reduced in number, but those present showed no lesion marked enough to have survived 24 hours autolysis.

Kidneys. Together weighed 270 g. (normal). The surface was finely granular, the cut surface pale with obscured markings. Microscopically, a
severe glomerular lesion of Kimmelstiel-Wilson type was present (Fig. 1). Nearly every glomerulus showed balls of aniline-blue staining material in the centres of its capillary loops. Fuchsinophilic material and crescentic caps were rare. Complete obliteration of many glomeruli had occurred. The vascular lesions were those of mild hypertension only.

Endocrines. Pituitary contained a single small infarct scar (Fig. 6). Thyroid inactive but within normal limits. Adrenals contained one 15 mm. cortical adenoma.

Nervous system. Spinal cord (five levels) normal (Fig. 2). Posterior root ganglia (four examined), normal. Radial (Fig. 4) and phrenic nerves normal. Sciatic nerves no obvious demyelination, but marked sclerosis of small arterioles (Fig. 5). Posterior tibial nerves showed a severe degree of demyelination (Fig. 3) a large proportion of the myelinated fibres having been lost. Permission to open the skull was not obtained till the fourth day after death; because of this no microscopic examination of the brain or the retina was attempted. The brain however was macroscopically normal and its vessels little diseased.

Summary

1. Benign hypertension, coronary obstruction, myocardial infarct.
2. Diabetic nephropathy.
3. Peripheral neuropathy.

Comment. There is no doubt that the nervous lesion is a pure peripheral neuritis, with no central involvement. The vascular lesions in the sciatic nerve are probably sufficient to account for them, in this case at least. The distribution of vascular lesions is curiously irregular in this case, as often in diabetes.

The renal lesion is unusual in that the very severe ball lesions are not associated with any fibrinoid-lipoid material. Fibrinoid is also absent in the afferent arterioles, and it is possible that both these negative features are associated with the absence of severe hypertension. Hall (1952) has described conspicuous atheroma of the renal arteries as common in the Kimmelstiel-Wilson kidney, but though we have been familiar with his work for some time, this is the first case in which we have seen anything resembling the lesions he describes; it is of note that the part of the kidney supplied by the renal artery division chiefly affected is macroscopically indistinguishable from other areas.

Discussion

DR. FRASER: I suppose this is as you say, Dr. Lennox, a very typical case of diabetic nephritis and also of diabetic neuritis, with all their clinical features, but it is unusual not to have hypertension—I have not any very serious suggestion to offer to account for that. I think perhaps as it is unusual to find such severe neuritic involvement in these cases we might discuss that first. Incidentally, I did not gather whether this neural lesion you saw had any exudates around it, such as you see in the retina or the kidney, Dr. Lennox?

DR. LENNOX: I saw no sign of any.

DR. FRASER: Well, I would like to suggest that to start this discussion, as we have here Dr. M. M. Martin from King's College Hospital, who is studying diabetic neuritis, he might like to make some comments on it.

DR. MARTIN: I have enjoyed very much listening to what has been said so far. I would like to say, first of all, that Dr. Fraser stressed that the C.S.F. protein was normal. This is not very unusual. In a large series of cases of diabetic neuropathy where C.S.F. examination was carried out, the protein was raised in only 30 per cent. of cases. There does not seem to be any close relation between the protein level and the severity of the clinical syndrome or the presence of posterior column lesions or any other clinical manifestation. It has been stated (Rundles, 1945) that the C.S.F. globulin is always raised, but there again all we have been able to show is that if the case is a very severe one the protein and globulin are usually raised; but we have seen very severe cases in which the protein and globulin were normal.

It has often been said that diabetic neuropathy and diabetic nephropathy constitute two parts of a single syndrome. I do not think that is true; both these degenerative conditions may be found at times in one person simply because both result somehow from the disturbed carbohydrate metabolism of diabetes mellitus. In a series of 150 cases of diabetic neuropathy we have only been able to find one case of the full-blown, typical clinical picture of Kimmelstiel-Wilson syndrome.

As regards the pathology: all the evidence on the pathology of nerve lesions which has been published is based on postmortem investigations. As diabetic neuropathy is not in itself a lethal disease, the subjects are usually elderly and it is not therefore surprising that evidence of arteriosclerosis was found in most cases. It is only one step further to say that the neuropathy is due to arteriosclerosis of the vasa nervorum. We have tackled the problem by carrying out nerve biopsies on patients with neuropathy, both young and old. The nerves we removed were either the digital branch of the anterior tibial to the adjacent sides of the 1st and 2nd toes, or the sural. The disability which remains is very slight: there is to begin with some numbness, but in practically all
Fig. 1.—Kidney. A severe and extensive Kimmelstiel-Wilson lesion, with 'balls' of aniline-blue-staining material in the centre of practically every capillary loop. A minority of glomeruli are completely obliterated. (Picro-Mallory x 125.)

Fig. 2.—Spinal cord. The areas of pallor seen are well within normal limits. (Weigert-Pal x 9.)

Fig. 3.—Posterior tibial nerve. Well-marked demyelination: most of the bundles have lost more than half their myelinated fibres. (Weigert-Pal x 33.)

Fig. 4.—Radial nerve. Control for previous figure. Normal myelination. (Weigert-Pal x 33.)

Fig. 5.—Sciatic nerve. Medial hyalinization and intimal thickening in arterioles. (Picro-Mallory x 205.)

Fig. 6.—Pituitary. The scar of an old infarct in the anterior lobe. This is one lateral half of a horizontal section through the whole gland, with the posterior lobe lying to the left. (H. and E. x 13.)
the patients there was complete recovery within three months—so such nerve biopsies can be carried out, in spite of Joslin's (1947) contention that they are not feasible and always lead to paralysis. We found on examining the nerves a considerable degree of both myelin and axis cylinder degeneration and, although actual counts have not yet been done, there appears to be a correlation between the degree of degeneration and the severity of the case. As far as the vessels are concerned, we have quite often seen nerves with a considerable degree of degeneration, but with perfectly healthy and normal vessels; while we have also material from cases of occlusive vascular disease where the vessels are practically completely occluded and yet the nerves are normal, both as regards myelinization and axis cylinders. One very interesting thing we came across: it has been suggested (Treusch, 1945) that the non-myelinated fibres may be the first affected in diabetic neuropathy; and certainly the onset of the condition, very often with burning paraesthesia and ill-localized pains, strongly suggests involvement of the grey non-myelinated nerve fibres. On comparing horizontal sections of normal nerves and nerves from our cases of diabetic neuropathy, we found that while the myelinated fibres appear to be only slightly reduced, the little black dots one always sees lying amongst the myelinated fibres in the normal silver-impregnated section, i.e. the non-myelinated fibres, had practically disappeared from the pathological sections. I do not want to stress this too much at this stage, but it does appear that the underlying pathological process of diabetic neuropathy somehow affects the grey non-myelinated fibres first, before the larger (A and B) myelinated fibres. There is other evidence for this: we have carried out studies of vasomotor function in diabetic neuropathy and found it impaired in every case. Furthermore, vasomotor paralysis was found in cases with neuritic symptoms, but no signs on neurological examination, suggesting a relation between pain and non-myelinated fibre damage.

DR. LENNOX: I think there is one obvious criticism of Dr. Martin's observations on the arteries in polyneuritis. I do not think the fact that you find normal arteries in a nerve biopsy in the toe means that the primary lesion is not arterial. After all, if you get an arterial lesion in the sciatic nerve anywhere down the yard or more of nerve fibre, degeneration will follow in the peripheral part of the nerve. In polyarteritis presumably something exactly like that happens—vascular damage in the sciatic nerve for instance, resulting in peripheral nerve degeneration. I think your observation that you can get gross ischaemic damage to the limb without the appearance of peripheral neuritis is much more significant. Does peripheral arteriosclerotic gangrene ever start with the symptoms of peripheral neuritis?

DR. MARTIN: I do not think so, if it is pure ischaemia. I have been trying to see as many cases of occlusive vascular disease as possible both diabetic and non-diabetic. The only peripheral nerve damage in these cases seems to be confined to the area of grossly impaired blood supply. An area which is cyanotic and cold is, generally speaking, hypalgiesic and hypaesthetic. Interestingly enough, in cases of occlusive vascular disease the area of hypaesthesia (that is to say, impairment to cotton wool) is always of greater extent than the area of hypalgiesia, while in cases of diabetic neuropathy impairment of pin-prick extends over a far greater area than impairment to cotton wool. That tallies with the loss of the grey C fibres in diabetic neuropathy. We know that the pain of a pin-prick—I am not talking now of the sharp immediate sensation, but of the longer-lasting unpleasant pain sensation—is carried by C fibres, whilst cotton wool sensation and touch localization is carried by A and B fibres. Experiments by Lewis and Pochin (1938) and by others have shown that ischaemia damages the large fibres first and the C fibres survive longest. If I am right in saying that in diabetic neuropathy the C fibres are involved long before the A and B fibres, this supports the idea that the damage is due to metabolic disturbance and not to ischaemia.

The finding of normal ganglia and normal cord was satisfactory. So far as I know, in all cases where the cord has been abnormal the ganglia have also been abnormal and this constitutes further evidence that the lesion is primarily peripheral. If the degeneration is sufficiently severe, it will ascend to the ganglion and may spread further to involve the posterior columns and possibly the anterior columns. This would account for cases of anterior and ascending anterior neuropathy which have been described in cases of diabetic neuropathy.

PROF. DIBLE: I do not like the vascular explanation of the neuritis any more than anyone else does, except perhaps Dr. Lennox; because in the ischaemic limbs which I have examined, and I have done a very large number now, in the case histories, at any rate, there is no talk at all of the symptoms of peripheral neuritis, and in many of these the vascular changes are extreme, leading to gangrene.

DR. LENNOX: I would agree, sir. I was merely presenting what evidence there is for the vascular story. Is it not possible, though, that there is something about the distribution? After all, the distribution of arteriosclerosis in diabetes is ab-
normal. It is remotely possible that it might pick on the nerves first. After all, is not the origin of gangrene in the arteriosclerotic limb largely related to the fact that the skin loses its blood supply before other areas? Perhaps in ordinary arteriosclerosis while the skin loses its blood supply the nerves retain a relatively good one, and one would then have to assume that in diabetes the opposite occurred.

**Dr. Martin:** Well, there are two types of ischaemic extremity, the painful ischaemic foot and the painless ischaemic foot. In the one case the foot is cold, usually bright pink and extremely painful, suggesting that the nerves have been less damaged than the superficial structures which are showing the incipient gangrene, while in the second case the foot is cold, pale and quite insensitive and painless, showing that ordinary ischaemia can affect nerve function as well.

**Dr. Fraser:** Perhaps Dr. Gilliland would like to comment on this point, and perhaps he would mention the question of the associated retinitis, which I think would distinguish the arteriosclerotic cases from the neuritic cases, would it not?

**Dr. Gilliland:** I think it probably would, but I think it is only fair to say that ischaemia cannot be the only cause of the neuritis, because it is essentially so recoverable. Recovery is perhaps never perfect, but you can see a very great improvement—as this man showed; he was hardly able to get into the ward when we saw him first for ataxia and weakness, and in the later days he was walking quite well. One or two other points I would like to make: he shows, for instance, a typical history for these cases in that he had diabetes for a long time; usually it extends over eight years or more. He also undoubtedly neglected himself. He admitted that he had neglected himself and gave his job as the reason; he was a cook and said that he had to taste things constantly and so could never stick to a diet! The other thing that is remarkable is the time he lived after the diagnosis had been made. It is not usual for people with nephropathy to survive more than two years after diagnosis. Possibly that was due to the fact that, though his blood pressure rose from the time we first saw him—from time to time he had levels which seemed hypertensive—his final level was not clearly raised; that, of course, can be related to the absence of the necrosis of arterioles that we see in the usual case. Finally, I would like to ask if the little necrosis in the pituitary is the sort of thing that might have arisen during one of his severe hypoglycaemic attacks, on the same basis as those that arise from shock of any sort?

**Dr. Fraser:** Perhaps Dr. Doniach could answer that.

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**Dr. Doniach:** Yes, I think it could.

**Dr. Fraser:** Have we seen it before? It is not in the books.

**Dr. Doniach:** We have one case in our records where the necrosis was rather more widespread than this, an acute infarction.

**Dr. Lennox:** In hypoglycaemia?

**Dr. Doniach:** I think the case was one of diabetic coma, not hypoglycaemia.

**Dr. Fraser:** Perhaps he was both! Dr. Martin, you haven't any comment to make on the diarrhoea have you? No new evidence on that?.

**Dr. Martin:** No, not really. I have seen quite a number of cases of what I call "diabetic nocturnal diarrhoea"—it is not a new name, but I think a good one. Attacks nearly always follow a spell of poor diabetic control and characteristically it starts in the night, commonly about 2 a.m. Often the patients are free of diarrhoea during the day, and it is always worse at night—often up to 30 motions in a night. It is often associated with nocturnal incontinence which is uncommon in any other type of diarrhoea, infective or otherwise. Once the diabetes is stabilized the attacks become shorter, less severe and the interval between the attacks longer. It does seem that this nocturnal diarrhoea may be a neuropathic manifestation associated with the normal shift to what might be called parasympathetic dominance during sleep, and the barium meal studies seem to support that, but we haven't any really conclusive evidence.

**Dr. Fraser:** Have you established that folic acid doesn't do any good?

**Dr. Martin:** We haven't been able to show that it does. At one stage I thought pancreatic extracts were of value and they certainly did seem to work for a while, but then some of the patients relapsed again. Unfortunately, it is very difficult to assess any form of treatment because many patients improve spontaneously and one is very easily led up the garden path. Recently we tried some patients on ephedrine with the idea that this is a parasympathetic manifestation, and they certainly did seem to improve. But I don't want to say yet that ephedrine is a cure.

**Dr. Doniach:** I would like to ask Dr. Clarke if similar attacks of diarrhoea have ever been seen in syphilitic tabes?

**Dr. Clarke:** As far as I know, not, except perhaps in rectal crises. About the diarrhoea, I think that there is some association between it and the neuropathy. Rundles (1945) who had 125 cases, thought quite definitely there was a greater incidence of altered bowel function in his cases of neuropathy than in a normal diabetic population and he linked up also the urinary disorders. He thought there was a raised incidence of incontinence, as in this case, and of various
other sphincter disturbances, in his cases of neuritis. It has been postulated that this is evidence that the autonomic nervous system is also affected by the neuritic process.

DR. LENNOX: Since Dr. Martin has raised the matter of the metabolic origin of the neuritis, could I ask one question? In respect of the points on which he makes the distinction between nerve lesions in ischaemic limbs and nerve lesions in diabetes, is there any similarity between diabetes and beri-beri, which is presumably a metabolic disorder. Does beri-beri affect C fibres, for instance?

DR. FRASER: And arsenical neuritis, you might add.

DR. MARTIN: I'm afraid I don't know whether the C fibres are affected in either of those. In both arsenical neuritis and beri-beri the lesion is known to be associated with a disturbance of pyruvic acid metabolism. In beri-beri the deficiency of phosphorylated B1, the carboxylase, leads to an accumulation of pyruvic acid and arsenic produces a similar effect by damaging the protein component of pyruvic oxidase. The actual lesion appears to be at the same level in both conditions. As far as diabetic polineuritis is concerned, B1 deficiency has often been thought responsible and Markees (1949) has recently suggested that in Switzerland diabetics are usually short of B1. We have carried out tolerance tests on diabetics by injecting pyruvic acid intravenously. It looked at first that there may be something to support Markees' theory. We found that the shape of the curve was similar in normals and in diabetics, with or without neuropathy; there was, however, a slightly higher end-point in the diabetics especially in those who tended to become ketotic. Lestradet and Guest (1951) in America have since published an excellent paper which proves that the high levels of blood pyruvate found in ketosis were due to aceto-acetic acid, which is also measured by the usual Friedemann and Haugen (1943) method. Using Guests' modification which avoids this error we have shown that pyruvic metabolism is quite normal in cases of diabetic neuropathy.

DR. SHERLOCK: Ketones are the main interfering substance in the usual method. The type of diabetic who suffers from neuropathy rarely goes into ketosis. Surely the usual pyruvate tolerance test can be used in these patients?

DR. MARTIN: The patients become ketotic during the test. You cannot keep them on insulin because insulin will increase the carbohydrate breakdown and raise the blood pyruvic acid, so these patients have to be kept off insulin, and if they are kept off insulin, particularly if severely diabetic, they will soon develop ketosis.

DR. SHERLOCK: But the standard test surely is to give glucose and then measure blood pyruvate. I would have thought that a few hours off insulin before the test would have been sufficient.

DR. MARTIN: But the glucose test doesn't work very well in diabetics because there is such a high blood sugar level already, and also because if you raise the blood sugar above 400 mg. per cent. you get a rise in pyruvic acid, whether you give insulin or not. Apparently the pressure head of sugar will increase the level of pyruvic acid.

PROF. KING: That's a true bill—it really is pyruvic acid, is it? You say you get a raised blood pyruvic acid when you get 400 mg./100 ml. of blood sugar, but are you sure it really is pyruvic acid you are estimating?

DR. MARTIN: Yes, by the method used.

PROF. KING: Using Guest's modification?

DR. MARTIN: No, Guest's modification was only used in cases of diabetic neuropathy—not anything else, apart from some normals for comparison.

PROF. KING: In the presence of all that ketonic acid in the blood, any method for pyruvic acid must be suspect.

DR. MARTIN: Well, Guest claimed that by heating he could get rid of the aceto-acetic acid which interferes with the estimation of pyruvic acid and he has shown that in cases of diabetic coma, for instance, where the Friedemann and Howell method will give levels of 3, 4, 5 mg. per cent. (as Gilliland and I (1951) have shown before) the modification would show a level of round about 0.9 to 1, which is quite normal. In every one of our estimations the discrepancy does seem to have been corrected by heating for one hour.

PROF. KING: Is that in the cases with high blood sugar or cases of ketosis?

DR. MARTIN: The ketotics. There is one last question I should like to ask Dr. Fraser, and that is in connection with low 17-ketosteroids. Low 17-ketosteroids are usually found in cases of diabetes whether they have any nervous disability or not, and it has been said that it is due to a low output from the testicles. That does not seem to be right, because this present case has an output which is far below that of the adrenals alone, if one compares it with the normal female. Examination of seminal fluids has shown normal spermatozoa, although reduced in number in many diabetic males even in the presence of reduced androgenic excretion. Have you any views?

DR. LENNOX: Could I interject one small point? I nearly showed the testis in this case as an example of a fact that even at the age of 66, after a long and serious illness, one may still have an occasional spermatozoon!
Dr. Fraser: As for the ketosteroid level, such low levels are common enough in diabetes, but I think in any illness sufficiently impairing to general health you might equally well find the same. I do not think it is possible to determine from the level whether it is due to adrenal or testicular defect or both. These patients commonly have impotence, but there is no evidence that the impotence is related to the ketosteroids. You can give testosterone without effect.

Well, this has been all very interesting. We have learnt a good deal about diabetic neuropathy, but I think we have still a lot to learn about its cause.

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