STUDIES IN GLYCOSURIA AND DIABETES IN NON-WHITE POPULATIONS OF THE TRANSVAAL

PART I. AFRICANS

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In 1960 the non-White population of the Transvaal consisted of about 4,600,000 Africans, 105,000 Coloured and 62,000 Indians. The great majority of the two latter communities and about 40% of the Africans are urbanized.[1] Most of the work on diabetes has been undertaken among the Africans living in and around Johannesburg, and the Indians. Little is known about the rural African. Our experience of Coloured diabetics is limited, but we have no reason to believe that they differ significantly from their far more numerous fellows in the Cape, who are the subject of Dr. Jackson's papers in this issue.

DIABETES IN THE URBANIZED JOHANNESBURG AFRICAN

Most of the 800,000 Johannesburg Africans are manual labourers of low socio-economic status. Many, however, are rapidly becoming westernized, their living standards are rising, and a middle-class is emerging. The average diet is high in carbohydrate (maize, sorghum, potato, bread, sugar) and low in animal protein and fat. Hospital services are largely provided by Baragwanath Hospital, which has 2,200 beds.

Prevalence

The true prevalence of diabetes in the African is unknown. Most surveys thus far have been based on hospital populations and, to a greater or lesser extent, are biased. In an investigation of 2,122 ambulant African subjects (1,078 males and 1,044 females) attending the casualty department of Baragwanath Hospital, Seftel and Abrams[2] discovered 18 new diabetics—a prevalence of 0·85%. Most of these diabetics were middle-aged or elderly females and the majority were overweight. In addition to the new cases, 9 known diabetics were detected, bringing the total to 27 or 1·2% of the series. Politzer and Schneider[3] surveyed 3,121 African outpatients (2,006 males and 1,115 females) attending the Johannesburg Non-European Hospital, and found 18 new diabetics, a prevalence of 0·58%. In a study of 300 African old-age pensioners, Seftel, Keeley and Walker[4] discovered 12 diabetics (4%), 7 of whom were new. Even allowing for bias, these figures demonstrate that diabetes is by no means rare in the Johannesburg African and, although directly comparable data are not available, they suggest a prevalence that may be as much as one-half that of British or American Whites.[5] They readily explain the rapid growth of the Baragwanath Hospital diabetic clinic, which, since its inception in 1958, has registered nearly 700 cases. By contrast, the disease appears to be uncommon in the rural African. No surveys have been undertaken in the Transvaal, but in Basutoland Politzer, Hardegger and Schneider[6] studied 3,000 rural subjects attending the outpatient department of a mission hospital, and found a prevalence of 0·23%. In the Thaba Nchu district of the Orange Free State Walker[7] examined 500 subjects but failed to detect a single case of diabetes. Campbell,[8] also, has commented on the rarity of diabetes in the rural Natal Zulu. The reason for these urban-rural differences is obscure. There are numerous differences, both medical and social, between urban and rural Africans, but present knowledge is insufficient to indicate which of these are important in giving rise to diabetes. It is also worth noting that a higher urban than rural prevalence of diabetes is not peculiar to Africans; a similar situation exists in White populations.[9] The most plausible explanation would be to relate the higher urban prevalence to a higher incidence of obesity in city dwellers, who are assured of a more abundant and regular supply of food and who lead a more sedentary existence. Slome *et al.*[10] showed that both male

and female Zulu adults living in Durban were more obese than their rural fellows. This was especially true of the urban females, who were more than 30 lb. heavier than the rural women. In fact, the Durban Zulu women were found to be overweight much more commonly than women in the United States of America.

Clinical Features[11]

Among urbanized Johannesburg Africans the female diabetics outnumber the male in a ratio of 1·6:1, and about three-quarters of cases are over 40 years old at the onset of the disease. An intriguing feature is the great rarity of the disease in the first decade of life. We have still to encounter an African case in this age group.

The majority of the maturity-onset diabetics, especially the females, are overweight, their diabetes is relatively mild, ketosis is infrequent, and there is a tendency to insulin resistance. Those under 40 are thin, fat, or of average build, their diabetes is often severe, ketosis is common, and they are usually sensitive to insulin.

Socio-economically, African diabetics tend to be more advanced than average. Nearly 15% of one series of 250 cases were skilled workers, which figure was more than twice that found in a control group. In the same series, the tribal distribution and parity of the diabetics were similar to those of controls.[11]

Most of our diabetics deny a family history of the disease, but the reliability of this is questionable. Interestingly enough, we have seen at least 5 pairs of connubial diabetics, in none of which was the marriage consanguineous. An investigation of the distribution of the ABO and Rh blood groups in our diabetics is proceeding; preliminary results have revealed no difference from a control population.

Prompted by the suggestion that low tissue levels of the thiol compound (reduced glutathione) might be diabetogenic,[12] an investigation was undertaken of the incidence of glucose-6-phosphate dehydrogenase deficiency in African diabetics.[13] This genetically determined enzyme defect is present in 3% of South African Bantu males,[14] and affected individuals probably have a low content of reduced glutathione in their tissues. The activity of the enzyme was measured in 97 cases (52 males and 45 females), but only 2, both males, were found to be deficient. It was concluded that the great majority, if not all, cases of diabetes in Africans are unrelated to glucose-6-phosphate dehydrogenase deficiency.

All the *complications* of diabetes are found in the African patient, the commonest being ketosis, cataract and infection.[11] Diabetic coma and precoma are frequent and, despite intensive therapy, the mortality rate is very high. Ketosis is, in fact, the major cause of death in the African diabetic. The main reasons for the high mortality are the late presentation—it is not uncommon to obtain a history of disturbance of consciousness commencing 12, 24 or even 36 hours before admission to hospital—and the frequency of associated complications such as infection or liver disease.

Infections of all types occur, but the commonest are tuberculosis, pyogenic or fungal diseases of the skin, and urinary-tract infections. In one series 9% had pulmonary tubercle.[15] In our haemochromatotic diabetics (see below) as many as one-third develop tuberculosis. Reef and Heimann[16] have seen several cases with cavernous-sinus thrombosis caused by mucormycosis. This fungal invasion of the sinus was always found in patients with ketoacidosis, and it appears that most, if not all, such cases are fatal unless vigorously treated with an antifungal agent such as amphotericin.[17]

It is usually in the middle-aged or elderly that cataract is seen, but about 10% of cases are under 40, and the youngest has been a girl of 17.

Most interesting, perhaps, is the changing picture in regard to the vascular complications. In an earlier analysis of 250 cases admitted to Baragwanath Hospital during the period 1951 - 57, it was found that vascular disease was uncommon, but it was predicted that with time this complication would become increasingly manifest.[11] This appears to have happened. Since 1958 we have seen increasing numbers of patients with diabetic nephropathy, retinopathy, peripheral vascular disease and gangrene, and even myocardial infarction. We had not encountered a single example of the last complication in an African diabetic before 1958, but since then there have been at least 4, and possibly 6, cases.[18] Underlining this trend, are the preliminary results of a cardiovascular survey of 52 diabetics (32 females and 20 males) in whom the disease had been present for 3 or more years, the average duration being about 7 years. Diabetic retinopathy was found in 45% of cases, hypertension—defined as a diastolic pressure greater than 95 mm.Hg—in 50%, proteinuria in 25%, an impalpable dorsalis pedis or posterior tibial pulse in 20%, and electrocardiographic evidence of myocardial ischaemia in about 8%. The mean serum-cholesterol level for the females in the group was 246 mg.%, and the males 222 mg.%. The male and female serum-uric-acid levels were 5·6 and 4·6 mg.% respectively. These biochemical values are about the same as those of non-diabetic Africans of similar age and socio-economic status.[19]

We have seen one patient who presented with the nephrotic syndrome, and diabetes, which was very mild, was discovered only after renal biopsy had revealed the typical nodular and diffuse lesions of diabetic glomerulosclerosis.[20]

A fair number of pregnant diabetics are seen and the complications, both maternal and foetal, are similar to those found in White subjects. The foetal mortality is high, mainly because it is difficult to maintain strict diabetic control throughout pregnancy in patients who very often are illiterate and poor.

Several workers have demonstrated a significant association between diabetes and cancer of the corpus uteri,[21] a condition in which there is some, but by no means conclusive, evidence that excessive or prolonged oestrogenic activity is an important aetiological factor.[22] It is therefore of some interest that de Waard,[23] using a cytological method to assess oestrogenic activity, found a much higher level of activity in our African diabetics than in non-diabetic controls. He further showed that the higher activity was probably not due to the diabetic state *per se*, but was related in some way to the associated obesity and hypertension, both of which are commoner in diabetic than non-diabetic subjects.

The Haemochromatotic Diabetic

Thus far the picture of diabetes in the Johannesburg African is very similar to that seen in White populations. A striking difference, however, is the frequency with which the African suffers from diabetes caused by an acquired form of haemochromatosis.[15,24,25] It is well known that siderosis is very common in Johannesburg Africans.[26-29] Bothwell and Isaacson[29] showed in postmortem studies that 70% of adult males and 25% of adult females have excessive deposits of iron in their tissues. In most cases the iron deposits are confined to the liver and reticulo-endothelial system.[28,29] In a significant minority, however, the iron is present not only there but also in a number of epithelial tissues such as pancreas, thyroid, adrenal, pituitary, testis, salivary glands, gastric mucosa, and heart muscle—a distribution identical with that found in the condition of idiopathic haemochromatosis.[24] Two features of this African haemochromatosis deserve emphasis.

Firstly, apart from liver and spleen, the heaviest deposits of iron are found in the pancreas, both the acinar and islet cells being involved. Secondly, the haemochromatosis is always associated with hepatic cirrhosis, usually portal in type. In fact, it was found that all Africans with portal cirrhosis and moderate or marked siderosis of the liver had haemochromatosis.[24]

There is now good evidence that the major source of the iron deposited in African haemochromatosis is locally brewed alcoholic concoctions such as kaffir beer and its numerous variants.[30-32] These brews are markedly acid in reaction and readily corrode the crude iron containers (petrol drums, paraffin tins) in which they are usually prepared. They thus attain high iron concentrations, which average about 4 mg.% and are sometimes as high as 10 or 15 mg.%. * Radio-iron absorption studies have shown that enough of this iron in the brews is absorbed to account adequately for the quantities of the metal that are found in the tissues at postmortem.[32] Thus haemochromatosis in Africans is an acquired condition, unlike idiopathic haemochromatosis of White subjects, which is generally attributed to a genetically determined defect of the iron-absorption mechanism and results in the excessive absorption of iron from a diet of normal iron content.

Idiopathic haemochromatosis is a well-known cause of diabetes in Whites. In both postmortem and clinical studies it has now been established that African haemochromatosis may also give rise to diabetes. In one study,[25] 20% of a series of African diabetics coming to necropsy were found to have haemochromatosis, a figure 7 times that of a control series. In another[24] it was shown that most Africans dying from portal cirrhosis of the liver were in fact suffering from haemochromatosis and that 22% of them had been diabetic during life, which is 10 times the figure for controls. In both studies every case of haemochromatosis associated with diabetes had chemical concentrations of iron in the pancreas within the range of those found in idiopathic haemochromatosis. Finally in a clinical study,[15] in which the diagnosis of haemochromatosis was based on a combination of serum-iron estimations and liver and gastric biopsies, 7% of an unselected group of African diabetic hospital patients were shown to be haemochromatotic (10% of the males and 5% of the females). These figures are extremely high when compared with the 0·08% incidence of idiopathic haemochromatosis in an American series of 50,000 diabetic subjects.[9] It should, however, be emphasized that the figures refer only to a hospital population and the incidence of haemochromatosis in the general African diabetic population may well be a good deal lower.

African haemochromatotic diabetics are generally easily distinguishable from their more numerous non-haemochromatotic fellows.[15] Most of them, although over the age of 40, are males who are thin or wasted. They are all consumers of alcoholic brews, all have firm hepatomegaly, and the majority show evidence of portal hypertension or liver failure. Porphyria cutanea tarda, either manifest or latent, is present in about one-third of cases. A similar proportion develop tuberculosis. The prognosis is poor, mainly because of the severity and rapid progression of the hepatic cirrhosis; additional factors are the background of alcoholism, the high incidence of tubercle, and the fact that in half the cases the diabetes is severe and difficult to control. Patients are liable to both ketosis and hypoglycaemic reactions to insulin. By contrast, the majority of non-haemochromatotic diabetics over the age of 40 are obese females, who infrequently imbibe alcohol and generally have little or no evidence of liver disease. Their incidence of tubercle is 9% while that of porphyria cutanea tarda at 2% is similar to the incidence in the non-diabetic African population over the age of 40.[24] Their diabetes is usually of mild or moderate degree, and their prognosis is much better.

The very high incidence of porphyria cutanea tarda in African haemochromatotics is unexpected, for the condition has not been described in White subjects with idiopathic haemochromatosis. African haemochromatosis differs from the idiopathic variety in the severity of the liver-cell damage and the invariable history of alcoholism; both these factors have been stressed in the pathogenesis of porphyria cutanea tarda.[35,36]

Treatment

Diabetics who are uneducated and whose diet for economic reasons consists largely of carbohydrate, require some modifications of the usual principles of therapy.[37] Most important is that attempts to render the urine sugar-free are not only impracticable but, in cases requiring insulin or certain oral hypoglycaemic agents, also dangerous, since they are very liable to result in hypoglycaemia. This, in view of the delay that the majority of African patients experience in obtaining medical attention, is not infrequently fatal or results in permanent brain damage. We aim, therefore, at the control of symptoms. To facilitate the early diagnosis of hypoglycaemia, and also of diabetic ketosis, all our patients are fitted with an irremovable wrist-bracelet marked 'DIABETIC'.

As elsewhere, therapy consists of diet alone, or diet plus insulin or oral hypoglycaemic agents. Of our patients in the diabetic clinic 13% are on diet alone, 42% are on insulin, and 45% are being treated with oral drugs.

(*a*) *Diet*. In view of the high carbohydrate content of the average African diet, most doctors in the past took a frankly pessimistic view of attempts to achieve dietary control in African diabetics. Accordingly, it was the custom to treat most cases with insulin in amounts designed to cover the high carbohydrate intake—a clearly undesirable situation, particularly considering that the majority of patients are overweight. At the diabetic clinic we renewed our efforts to achieve dietary control and, thus far, have met with a fair measure of success. Most of the credit for this must go to our Principal Dietitian, Miss H. C. Pledger. She undertakes a careful analysis of the diets the patients consumed before the discovery of their diabetes. She then prescribes such a diet according to age, weight and occupation as is within the economic means of the patient. The dietary instructions are given in great detail to each patient individually, and actual servings of prepared foods are demonstrated at the clinic. Simple exchange lists of foods are given. Additional protein is sup-

*It has been suggested that iron 'overload' is the primary cause of siderosis in the local African.[31,33]

plied as milk powder when necessary. Particular emphasis is placed on the proper distribution of the carbohydrate intake throughout the day. The urbanized African usually consumes the bulk of his high-carbohydrate diet at the evening meal, and in the diabetic this must result in nocturnal polyuria. By redistributing the carbohydrate intake so that the greater part is consumed during the day, when physical activity is greatest, nocturnal frequency is rapidly reduced.

(*b*) *Insulin*. This is self-administered in nearly all cases. African diabetics adapt themselves very well to the injection technique, and injection abscesses have been very rare. Most cases receive a single daily injection of lente insulin. In about 6% of the patients on insulin improved control was obtained by adding the oral agent metformin; all these cases were previously poorly controlled on 80 or more units of insulin daily.

(*c*) *Oral drugs* have proved a great boon to the African diabetic, and nearly half our patients are being treated with them. Of the cases on oral therapy 54% are receiving chlorpropamide and 44% tolbutamide. The former is the more potent and its single daily dose is an obvious advantage. On the other hand, the only serious hypoglycaemic reactions we have seen with the oral drugs have been in patients on chlorpropamide. For this reason we prefer to start with tolbutamide and change to chlorpropamide if the former is not effective. In rare cases, dyspepsia and sensitivity rashes have complicated therapy with these drugs. Jaundice has not been encountered. The third oral drug used in our clinic is metformin. Only 2% of all patients on oral therapy receive this alone. Much more commonly we use it to potentiate the effects of the sulphonylureas or insulin; 14% of patients on sulphonylureas and 6% of those on insulin receive metformin. In this supplementary role metformin is often very useful, and usually free of side-effects.

Most of our *pregnant diabetics* are treated with insulin. Two, however, have been given oral drugs; in both the diabetes was excellently controlled and normal infants were delivered after induction of labour at 38 weeks. The first patient, aged 40, received chlorpropamide throughout her pregnancy, 500 mg. daily during the first 5 months, and then 250 mg. daily until delivery. The second, aged 42, was treated with 20 units of lente insulin during the first trimester, and a combination of chlorpropamide, 250 mg. daily, and metformin, 500 mg. thrice daily, during the remainder of the pregnancy.

CONCLUSION

The pattern of diabetes in the Johannesburg African, the haemochromatotic minority apart, is clearly very similar to that of White populations. With further westernization and urbanization it is probable that the few remaining differences, such as the rarity of the disease in the first decade of life and the infrequency of complicating myocardial infarction, will disappear. It is also likely that the prevalence of the disease will eventually equal that of Whites.

We are grateful to the Superintendent of this Hospital, Dr. I. Frack, for permission to publish this paper. We are indebted to the following for technical and other assistance – Misses G. Schoen, P. Coles, A. Nurse, and M. Andre. The expenses of the investigation were met in part by a grant (H:4244) from the National Heart Institute, United States Public Health Service.

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