RECENT OBSERVATIONS ON ZULU AND NATAL INDIAN DIABETICS IN DURBAN*

G. D. CAMPBELL, M.B., M.R.C.P. (EDIN.), *Physician*, and JOHN MCKECHNIE, M.D., B.Sc. (HONS.), M.R.C.P. (EDIN.), *Registrar*

The Diabetic Clinic of the King Edward VIII Hospital, Durban, Natal

1. *Present Size and Rapid Growth of the Diabetic Clinic of the King Edward VIII Hospital*

It is just over 3 years since the establishment of a diabetic clinic in the MOPD of the King Edward VIII Hospital, and we have just registered our 3,000th new patient. At first, the clinic was held on a single half-day session weekly, since we had no idea of the large number of patients that we were going to collect. Within 4 months a second half-day was found necessary, and it is only by energetic manoeuvres, such as giving larger drug allowances, that we have been able to keep the attendances within reasonable limits. However, recently no less than 108 diabetics had to be seen by 2 doctors in a single half-day session, which is overstepping the bounds of reasonable, let alone good, medical practice.

* Paper presented at a Plenary Session, 43rd South African Medical Congress (M.A.S.A.), Cape Town, 27 September 1961.

Of the present total of 3,103 new patients, 545 are Africans — mostly Zulus, and 2,558 Natal Indians. Contrary to our previous expectations, there has been no falling off of clinic registrations of new patients, the rate today being greater than it was in the early days of the clinic. The monthly registrations of new patients in our first 3 years were 79, 79, and 88 patients respectively.

2. *The Incidence of Diabetes in the two Races*

We have not embarked upon incidence studies such as those carried out by our colleagues north of the Vaal River, who, judging by their lively journal correspondence, will be dilating upon this problem! On the basis of our observations we feel that diabetes would appear to be far more common amongst Africans in big-city dwellers[1] than in those that live in the countryside; in fact, we have noted a remarkably constant 'period of exposure' to town life, before the maturity-onset patient develops his diabetes — hence the 'rule of 20 years'. We have previously observed, on the basis of our new clinic registrations and the probable population at risk, that diabetes would appear to be about 8 times as common in Natal Indians as in urban-dwelling Africans.[2] This would fit in well with the figure of Seftel[3] of 1% for urbanized Africans in Johannesburg, and that of Wood[4] of 8·8% for Natal Indians in a sub-economic housing scheme. However, we now agree with Seftel's latest observations on Transvaal Indians,[5] that the figure of 8·8% is probably too low, in view of the fact that his series includes many Muslim (i.e. affluent) Indians, and we have shown (see below) how much greater the incidence of family histories of diabetes are in Muslims than in the poorer Hindu patients, who would have formed most of the population that Wood[4] sampled.

3. *Treatment of Diabetes*

Briefly, the diabetes of the Durban African resembles the syndrome seen in the European, with diabetic ketosis being an important problem,[6] — only 25% of patients, a smaller proportion than in Europeans, being truly dependent upon insulin. In the Natal Indian diabetic, ketosis is very uncommon, and less than 4% of the total patients require insulin.[2] We have had good results with the oral anti-diabetic agents even in young and pregnant diabetics, and on the strength of this latter response, we regard these patients as falling into a group that we have called the 'insulin-independent young diabetic',[7] a variant that, we have no doubt, will be described from many tropical and subtropical countries when the use of oral agents becomes as widespread in young diabetics as it is in Durban. In both races, with many underprivileged diabetics, the oral agents have for obvious reasons been a great boon, and we have used them on a very wide scale. It is to the use of these drugs that we ascribe the phenomenal growth of our clinic. At present, *inter alia*, we have 1,200 patients on chlorpropamide — the largest single series in the world — and 106 patients upon metformin, coincident with other drugs, especially chlorpropamide—a most valuable combination. The rest of the large number of patients at present on the sulphonylureas (about 400) are on tolbutamide. Our numbers are not accurate because, after 3 years of using tolbutamide, we are seeing increasing numbers of secondary failures with this drug. We have assessed the incidence of significant side-effects of sulphonylureas in a series of 2,061 patient-trials as being 1%[8] — metahexamide having been the chief offender. In common with many workers in the world today, we find that the serious effects from tolbutamide and chlorpropamide are equal, having had only a single very severe reaction with each drug. Metformin has been used in small doses without ill-effect. We have noted that it is very easy to talk patients out of many of the so-called 'side-effects' of the sulphonylureas— something that has also been remarked upon by other observers.

4. *The Nature of the Diabetic Syndrome in the Natal Indian*

Our widespread use of the oral agents has accentuated the very small percentage of Natal Indian diabetics who are truly dependent upon insulin — 4%.[2] In addition, their mild diabetic state has been shown to be particularly productive of severe and lethal diabetic vascular disease, morbidity, and mortality.[9,10] It has previously been noted from our clinic how many of our Natal Indian diabetics, of whatever age or sex, are short in stature, very fat (often with trunk and buffalo-hump obesity), hypertensive, possessed of white striae, resistant to and not dependent upon insulin and seldom becoming ketotic.[7] Furthermore, we reported[7] how commonly facial and body hirsuties have been seen, in extent and distribution resembling that of female pseudohermaphroditism in the European. In view of the widespread belief that this trait is very common among the Natal Indian females, we have recently found that the incidence of moustaches and 'sideburns' in 100 female Natal Indian diabetics was 74% and 50% respectively, and in 93 controls only 15% and 15% respectively.[11]

We previously attempted to tie up our clinical observations with those of Gillman and Gilbert[12] in their hypophysectomized, adrenalectomized and pancreatectomized baboons, and had come to the following conclusions:[7]

(*a*) The high incidence of insulin-independence and absence of ketosis would indicate, in these people, satisfactorily functioning islet cells, (or *vide* Vallance Owen,[13] low levels of antagonists or alternatively islets resistant to antagonists).

(*b*) The short stature and absence of ketosis would indicate low levels of growth hormone. (Tall Natal Indian diabetics are rare.) The hypophysectomized diabetic baboon only becomes ketotic when growth hormone is available.[12]

(*c*) The obesity, striae, hypertension, severe vascular disease,[10] insulin resistance, insulin independence, body and facial hirsuties (and again perhaps short stature) would point towards more than usual production of adrenal 'glucocorticoids' and androgens.

Thus we have a glycosuric syndrome probably characterized by normal insulin levels, low-growth hormone levels and high levels of certain adrenal hormones.

Furthermore, we have postulated a theory based upon Vallance Owen's observations to explain the fact that diabetic vascular disease may appear before glycosuria in the Natal Indian. We believe that there may be one or more antagonists with simultaneous actions upon the islet cells and the arterioles, the former resulting in glycosuria, and the latter specifically causing, or resulting in, 'diabetic' vascular disease. In other words, in African and European patients where 'diabetes' exists for some time before vas-

cular disease supervenes, the effect of the antagonists is first manifest in a failure of the 'islet cells', with glycosuria and the classical symptoms of diabetes. Because the vascular endothelium is hereditarily or racially relatively more resistant to the antagonists, vascular complications occur later. In the Natal Indian, however, the arterioles are far less 'sturdy' than the islet cells, and consequently it is not uncommon to see diabetes present as a retinopathy,[17] for instance, without even impairment of glucose tolerance, since the vessels 'give in' before the islet cells. These observations are borne out by the fact (only too well known to many insurance actuaries at their great cost) that the vascular tree of the Natal Indian is very brittle indeed, and even in the non-diabetic, the death rate from vascular disease in relatively young people is far greater than in other races. We believe that the high proportion of insulin-independence in the Natal Indian diabetic is a measure of relatively good function of sturdy islet cells. If we are to postulate an adrenal component to this diabetic syndrome, then we must remember Vallance Owen's observations[18] that his antagonists are dependent upon, and their action enhanced by, certain hormones, one of the chief of which is the adrenal contribution. We hope that in the very near future we will be able to avail ourselves of Dr. Vallance Owen's kind invitation to send him blood samples. It will be particularly interesting to see if he can find similar characteristics in our bloods and in the bloods of those rare European diabetics who develop vascular disease before glycosuria.

5. *Family Studies*

African diabetics, as do most Africans who are handled by doctors who speak their language, give an excellent family history, and though they have a fairly good idea of what constitutes diabetes, they are not nearly as well informed as the Natal Indian, who, strangely enough, takes about 4 visits to decide whether he has a family history of the disease — perhaps because it takes him some time to think about his myriad relations. Less than 4% of African patients in whom information was considered reliable, have a family history — the classical example being the Zulu Royal family in whom the disease is rife, both in direct and cadet lines.[1] In a previous study of 493 Natal Indian diabetics, we found a family history (excluding connubiality) of 47·8%.[14] Recently, a further 746 patients have been reviewed, and a total incidence of 45·6% obtained.[15] In both groups the incidence of family history was found to parallel social and economic status, the highest being found among the Muslim people, who, as is well known, are financially the best-off in the Natal Indian population.

We have been greatly stimulated by a study of diabetes in husbands and wives:[16] In our first 2,500 Natal Indian patients, we have managed to record family histories in about 2,000 patients. Amongst these we have found no less than 90 such connubial pairs, not all of whom have been attending the clinic and, in these, observations have been based upon one of the pair. (Frequently the one spouse has been widowed by diabetes in the other.)* Secondly, that emergence of diabetes in these pairs *may* be related to parity — even in the male partner.[19] This theory is not as strange as it may seem, especially in the light of Wexler's work in Cincinnati,[20] where he showed that atherosclerosis in the rat develops at the same rate in both parents, according to the number of litters. At present allylisothiocyanate is being fed to experimental animals, more particularly by Butterfield and his associates at Greys Hospital,[21] on the basis of our observations, and we await their results with interest. Anyone who has smelt or tasted this noxious substance would be surprised that it is not able to inhibit more enzyme systems!

6. *Studies of Fats, Fibrinolytic Activity, Serum Mucoproteins and Cholesterols in Natal Indian and Zulu Diabetics*

Recently Hathorn, Gillman and Campbell,[10] working in our clinic, took advantage of the remarkable discrepancy between the incidence of vascular complications in Natal Indian and Zulu diabetics to study in a large number of each group certain blood components, notably total fats, fibrinolytic activity, serum mucoproteins, and serum cholesterols. Briefly, it was found that in the Natal Indian (in whom diabetic vascular disease is probably four times as common as in the Zulu), the levels of total lipids, especially in females, were much higher than in the Zulus, and that these high levels appeared to be mirrored in poor fibrinolytic activity. In Zulus, fibrinolytic activity was much more effective and total fat levels lower. There was little difference between cholesterol levels in either the diabetic groups or in the large number of controls. Interestingly enough, contrary to figures reported for Europeans with vascular disease,[22] serum mucoproteins were raised in neither diabetic group. In the light of these findings, it is interesting to note that the incidence of objective diabetic neuropathy is 15 times higher in the Natal Indian than in the Zulu, and one wonders just what part the vasa nervorum play in the genesis of this syndrome.

It would appear highly likely (on the basis of these blood studies, and the observations upon diabetic vascular disease in the Natal Indian by Cosnett[9] and McKechnie,[23] and in the Zulu by Campbell[6]) that increased vascular involvement in diabetics of the same duration of disease would appear to correspond with higher total lipid levels and poorer fibrinolytic activity in the blood.

7. *Triparanol ('Mer 29')*

Melby *et al.*[24] reported that triparanol (Mer 29) has an inhibitory action upon adrenal steroid synthesis, if given in a sufficiently large dose (1 G. daily). In view of our belief that the adrenals play a predominant part in the syndrome of diabetes in the Natal Indian, we were anxious to assess the effect of Mer 29 in our patients. In 12 patients the drug was given in a dose of 500 mg. twice daily, without adjusting previous anti-diabetic therapy. We obtained

* The following late addition should be read as part of the text: At first[16] we were inclined to think that this phenomenon was merely a reflection of the high incidence of diabetes in the Natal Indian race, but for the striking way in which many of these pairs developed diabetes simultaneously or almost simultaneously after between 15 and 55 years of marriage. Furthermore, many of these pairs had no family history of diabetes. We postulate two possible theories if this connubial emergence is not the result of a high incidence of the disease: Firstly, that some article of foodstuff may be incriminated, especially in view of this almost simultaneous emergence; this we feel may possibly be the chronic ingestion of mustard oil (allylisothiocyanate)[17] which may conceivably come into the category of a 'thiol immobilizer'[18] as it appeared to be in the 'epidemic dropsy' of Bengal.[33]

most significant improvement of control in 7 patients, with complete clearing of glycosuria after about 5 days of treatment. It should be added, though, that glycosuria is seldom completely cleared even in 'well-controlled' Natal Indian diabetics. There was, of course, no change in dietary regimen during therapy. The serum cholesterol fell markedly in all patients and the uric acid decreased significantly in 7. These results in our very small series are interesting, and one wonders whether Mer 29 or a similar substance will not find a place in the treatment of diabetes, in particular in those syndromes (seen in the Natal Indians) in which we believe that the adrenal may be more than ordinarily implicated.

8. *Uric-acid Studies*

The Natal Indian suffers from a rather common and often very severe gout syndrome, and in view of the suggestion of Lazarow[27,34] that an intermediate product of uric-acid metabolism may be diabetogenic, we attempted (after the manner of Herman, of Cape Town,[28] and Beckett and Lewis, of London[29]), to see whether we could confirm their findings in Natal Indian diabetics. Herman noted a significantly high incidence of abnormal glucose tolerance both in gouty patients and patients who were hyperuricaemic without gout. Nine of 26 hyperuricaemic patients had raised fasting blood sugars — a proportion that fits in well with Herman's findings.[28] Of 16 clinically gouty patients, 10 had abnormal glucose-tolerance tests, using the criteria of Lee[30] and Remein *et al.*[31]

In a series of 174 Natal Indian diabetics (102 females and 72 males), 10·8% of the males and 2·9% of the females had serum uric-acid levels of over 6·0 mg. %. Mean serum uric-acid levels for the sexes in this series showed higher levels in the males (4·24 as to 3·62 mg.) and higher levels for the females (3·56 as to 3·24 mg.) as compared with the findings of Beckett and Lewis[29] in their very large series of 812 diabetic patients. Further analyses of these and several other of our findings are being conducted and will be reported in due course.

CONCLUSION

What then are the main findings that we feel have been arrived at by our 3 years' study of non-European diabetics in Durban?

Firstly it would appear obvious that we have probably more clinical material for original research upon diabetes in the dark-skinned races in the tropics and subtropics, than is generally realized. This is borne out by the growing interest in tropical diabetes, which will reach its culmination with the publication of Prof. J. Tulloch's monograph on *Tropical Medicine* in the near future.

Secondly, we have in the Natal Indian race a most interesting and significant group of young diabetics who, though they have the classical symptoms and presentation of diabetes, are not truly dependent on insulin even whilst pregnant; these we have called 'the insulin-independent young diabetics'. We should like to say that we agree most wholeheartedly with Professor Tulloch in the sentiments he recently expressed,[25] when he dealt the deathblow to the so-called 'J' type of diabetic.

Thirdly, the possibility that the adrenal glands may be more than ordinarily incriminated in the diabetic syndrome in the Natal Indian is very exciting and merits further study.

Fourthly, will our very wide-scale use of the oral anti-diabetic substances stem the dreadful tide of diabetic vascular complications in the Natal Indian, to which, we believe, the unnecessary use of exogenous insulin may have contributed in the past?[17]

Fifthly, we can say with confidence, on the basis of our studies in the Durban African, that the rapidly advancing social and economic standards on the African continent will be particularly fruitful in regard to the emergence of diabetes.

Finally, we believe that our unique opportunity of studying large numbers of connubial diabetic pairs may help us to establish whether this may be due to the ingestion of a 'thiol immobilizer',[13] or to the as yet uninvestigated possibility that parity may have an effect on diabetic emergence in the male, or whether it is simply a reflection of a very high incidence of diabetes in the Natal Indian.

I think it will be agreed when we end by saying that Durban, apart from its other obvious attractions, is a diabetologist's paradise. It is a great shame that, whilst overseas clinics are embarrassed by superfluity of staff and replete with research grants, we should be unable to exploit more fully the potentialities of our clinic because of overwhelming new registrations of diabetics and gross shortage of doctors.

We should like to acknowledge the kind permission of Dr. S. Disler, Medical Superintendent of King Edward VIII Hospital in Durban, to publish this paper. We are particularly grateful to the many consultants of the hospital who have referred their diabetics to our clinic. We thank Drs. J. Davidson, B. Brokensha, and Brian Gibb for their great help in the clinic.

REFERENCES

1. Campbell, G. D. (1960): S. Afr. Med. J., **34,** 332.
2. *Idem* (1960): Bull. Intern. Diab. Fed., **6,** 50.
3. Seftel, H. C. (1961): S. Afr. Med. J., **35,** 66.
4. Wood, M.M. (1960): Med. Proc., **6,** 140.
5. Seftel, H. C. (1961): Personal communication.
6. Campbell, G. D. (1961): *The Zulu Diabetic.* Address, 4th Intern. Diab. Congress, Geneva; in print. Congress Proceedings.
7. *Idem* (1960): Brit. Med. J., **2,** 537.
8. *Idem* (1961): *Toxicity studies in very large-scale trials of sulphonylureas in non-Europeans in Natal.* Address, 4th Intern. Diab. Congress, Geneva. In print. Congress Proceedings.
9. Cosnett, J. C. (1959): Brit. Med. J., **1,** 187.
10. Hathorn, M. K. S., Gillman, T. and Campbell, G. D. (1961): Lancet, **1,** 1314.
11. McKechnie, J. (1961): Unpublished work.
12. Gillman, J. and Gilbert, C., Epstein, E. and Allen, J. C. (1960): Brit Med. J., **2,** 1260.
13. Vallance Owen, J. (1960): Brit. Med. Bull., **16,** 214.
14. Campbell, G. D. (1961): Medical Digest, Bombay. In print.
15. McKechnie, J. (1961): Unpublished work.
16. Campbell, G. D. (1961): Brit. Med. J., **1,** 1538.
17. *Idem* (1961): Med. Proc., **7,** 395.
18. Editorial (1961): Lancet., **2,** 87.
19. McKechnie, J. (1961): Unpublished work.
20. Wexler, B. C., Brown, T. E. and Miller, B. F. (1960): Circulation Research, **8,** 1.
21. Butterfield, W. J. H. (1961): Personal communication.
22. McKechnie, J. (1961): Unpublished work.
23. *Idem* (1961): *Ibid.*
24. *Idem* (1961): *Ibid.*
25. Tulloch, J. and MacIntosh, D. (1961): Lancet, **2,** 119.
26. Melby, J. C., St. Cyr, M., and Dale, S. L. (1961): N. Engl. Med. J., **264,** 583.
27. Lazarow, A. (1949): Phys. Reviews, **29,** 48.
28. Herman, J. B. (1958): Metabolism, **7,** 703.
29. Beckett, A. G. and Lewis, J. G. (1960): Quart. J. Med., **29,** 443.
30. Lee, S. T. (1960): Med. Clin. N. Amer., **44,** 1507.
31. Remein, Q. R. and Wilkerson, H. L. C. (1961): J. Chronic. Dis., **13,** 6.
32. Schwartz, C. T., Gilmore, H. R. (1958): Circulation, 18, 191.
33. Thompson, R. H. S. and King, E. J. (1957): *Biochemical Disorders In Human Disease,* p. 570. London: Churchill.
34. Lazarow, A. *In* Colowick, S., ed. (1954): *Glutathione.* New York: Academic Press Incorporated.