AN ANALYSIS OF THE RETINAL, CARDIOVASCULAR AND NEUROLOGICAL DISORDERS IN DIABETICS ATTENDING AN OUT-PATIENT CLINIC

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It is the purpose of this paper to report a preliminary analysis of the findings derived from a study of diabetic patients in Cape Town. For about 18 months a number of patients seen at the Groote Schuur Hospital Diabetic Out-patient Department have been asked to attend a special clinic held each week. At these sessions relevant historical data are recorded and a clinical and electrocardiographic examination is carried out. At each session an ophthalmologist has attended to record the ocular findings.

As the cases for this special clinic are largely selected at random by a social worker it is fair to presume that they are representative of the diabetic patients attending the hospital as out-patients. Approximately 2,000 patients are on the lists of the Diabetic Out-patient Department at present and of these about 200 attend the clinic each week.

The retinal, cardiovascular and neurological complications* occurring in 210 consecutive patients are considered in this analysis.

The Series as a Whole

The patients under review comprise 129 Europeans and 81 non-Europeans (54 Cape Coloured, 24 Malays and 3 Bantu).† 149 are female and 61 male, reflecting the greater number of women attending the Diabetic Out-patient Department as a whole.

Their distribution in 4 age-groups is as follows:

Group A: 19 years and under, 12 patients
Group B: 20 to 39 years, 20 patients
Group C: 40 to 59 years, 83 patients
Group D: 60 years and over, 95 patients.

In 156 patients the duration of diabetes was under 10 years and in 52 it was 10 years or longer.

As an arbitrary index of the severity of the diabetes the patients are divided into 4 groups according to their insulin requirements at the time of examination.‡ Their distribution in the 4 groups is as follows:

Group 1: Diet only, 54 patients.
Group 2: Diet and up to 20 units of insulin daily, 32 patients.
Group 3: Diet and 21 to 50 units of insulin daily, 81 patients.
Group 4: Diet and 51 to 200 units of insulin daily, 43 patients.

In none of the patients was the insulin requirement larger than 200 units daily.

Obvious difficulties are encountered in attempting an assessment of diabetic control. In the present series we have divided the cases into 4 groups, showing excellent, good, fair and poor control respectively. The assessment has been based on the following criteria:

Excellent: No hypoglycaemia. Glycosuria never more than 2 plus, usually nil. Fasting blood sugar 90-140 mg.%.

Good: Hypoglycaemia extremely mild and rare. Glycosuria nil to 2 plus, rarely 3 or 4 plus. Fasting blood sugar in the region of 170 mg.%.

* The vascular lesions of diabetes are probably not true 'complications'—they are more likely an integral part of the disease itself, but nevertheless the term is in general accepted and is convenient for use in this paper.

† For overseas readers: 'European' refers to all 'White' (Caucasian) persons. 'Non-European' refers to all others. 'Cape Coloured' refers to the Cape Province half-caste mulatto. 'Malays' are a special variety of the Cape Coloured, and are Mohammedans.

‡ The insulin requirement is no true indication of the severity of the diabetes, since a juvenile, ketosis-prone diabetic may take only 20 units, and a mild, obese, relatively resistant oldster may be uncontrolled on 200 units. Nevertheless we include analyses on this basis for want of a better one.

Fair: Occasional hypoglycaemia. Glycosuria variable, often 3 or 4 plus. No ketosis.
Poor: Liable to hypoglycaemia or ketosis or both not infrequently. Glycosuria constantly 4 plus.

In 197 patients adequate data was available for an evaluation of control. This was assessed as excellent in 57, good

TABLE I. THE RELATION BETWEEN RACE AND CONTROL

Control	*Europeans (White)*		*Non-Europeans (non-White)*	
	No.	*Percentage*	*No.*	*Percentage*
Excellent	45	34·9	12	17·7
Good	48	37·2	22	32·3
Fair	17	13·2	18	26·5
Poor	19	14·7	16	23·5
	129	100·0	68	100·0

in 70, fair in 35, and poor in 35 patients. The distribution of the control assessment separately considered for the two main racial groups can be seen in Table I.

In assessing the trends which appear in the analysis of complications in various groups certain general observations are pertinent.

1. Analysis (Table II) shows that in age-group D (60 years and over) there is a higher percentage of patients with diabetes of long duration as compared with age-group C (40-59 years). It would appear, therefore, that a high incidence of a complication in the older age-groups might equally be due to age or long duration of diabetes. On the other hand, the distribution of the age-groups within each 'duration' group—under 10 years and 10 years and over—is more complex. In the under-10-year group the percentage formed by the ratio of the two younger age-groups combined (25 cases) to the two older age-groups combined (131 cases) is 19·1%. The same percentage in the group with diabetes of 10 years and over is 15·6%. If, however, the composition of the two 'duration' groups is considered with regard to age-groups C and D, there comes to light a much greater discrepancy between the two 'duration' groups, there being a higher proportion of older (Group D) patients in the group with diabetes of longer duration. Therefore differences based on duration of diabetes might well be reflecting the effects of old age.

2. It is necessary to know whether the two racial groups differ materially in respect of duration of diabetes, age, sex, and control. These factors have been studied in the two racial groups and the main conclusions which emerge are as follows:

(*a*) Of the Europeans, 87 (67·4%) had had their diabetes for less than 10 years and 41 (31·8%) for a longer period than this; of the non-Europeans, 69 (85·2%) had had their diabetes for less than 10 years and 11 (13·6%) for a longer period than this. Among the non-Europeans, therefore, there is a higher proportion of patients with diabetes of less than 10 years' duration as compared with the Europeans.

(*b*) If the relationship between race and age is studied in Table II it will be seen that there is a relatively higher proportion of subjects in the younger age-groups among the non-Europeans included in this study.

(*c*) The sex ratio in the two main racial groups is as follows:

Europeans: 49 males, 89 females.
Non-Europeans: 21 males, 60 females.

Thus there is a relatively higher proportion of females in the non-European group.

(*d*) Table I indicates that a somewhat higher proportion of non-European patients fall into the less well controlled groups.

THE RETINAL COMPLICATIONS

It is generally agreed that the earliest stage of diabetic retinopathy consists of punctate micro-aneurysms in the vicinity of the macula. These may be accompanied by small discrete exudates, which may, however, be present alone. Later the exudates enlarge and coalesce to form characteristic irregular, homogeneous, yellowish-white patches. At this stage haemorrhages are present, initially small and round, but subsequently becoming irregular, larger and more numerous.

In the more advanced cases irregular dilatation and tortuosity of veins is seen, coils and loops may be evident, and finally more profuse retinal haemorrhages, vitreous haemorrhages, and the proliferation of newly-formed blood vessels and fibrous tissue, comprise the picture of retinitis proliferans. Subsequent contraction of fibrous tissue may result in retinal detachment.

The occurrence of haemorrhages or aneurysms was noted in 62 patients. In 42 of these, exudates were also present and in 7 additional patients exudates were observed in the absence of haemorrhages or aneurysms. In 3 cases retinitis proliferans was superimposed.

In 69 cases, therefore, diabetes was complicated by the specific retinopathy; 54 were female and 15 male. This

TABLE II. THE RELATION BETWEEN AGE AND DURATION, AND BETWEEN AGE, RACE AND SEX

Age		*Duration*					*Race*					
Group	*Total*	*Under 10 years*		*10 years and longer*		*Ratio* $\frac{+10\ yrs.}{-10\ yrs.}$	*Europeans*			*Non-Europeans*		
		No.	*% of total under 10 yrs.*	*No.*	*% of total over 10 yrs.*		*M*	*F*	*Total*	*M*	*F*	*Total*
A	12	11	7·1	1	1·9	9·1%	5	1	6	4	2	1
B	20	14	9·0	6	11·5	42·9%	5	4	9	3	8	11
C	83	65	41·7	17	32·7	26·2%	12	35	47	8	28	36
D	95	66	42·3	28	53·8	42·4%	18	49	67	6	22	28
Total	210	156		52			40	89	129	21	60	81

represents a total incidence of 32·9% and an incidence of 44·2% and 24·6% in the females and males respectively.

Separate consideration of the two main racial groups reveals that 37 of the 129 Europeans (21·7%) and 32 of the 81 non-Europeans (39·5%) showed retinopathy.

In respect of the four age-groups defined earlier we find 1 case in Group A, 3 in group B (15·0% of all patients in this age-group), 25 in group C (30·1%) and 40 in group D (42·1%).

In Table III the distribution and incidence with regard to duration of diabetes, insulin requirement and control is shown. In Table IV the distribution according to control of diabetes is separately considered in the two racial groups.

TABLE III. THE RELATION BETWEEN RETINOPATHY, DURATION, INSULIN REQUIREMENT AND CONTROL

	Total No.	*No. with retinopathy*	*Percentage with retinopathy*
Duration of diabetes			
Under 10 years ..	156	43	27·4
10 years or longer ..	52	26	50·0
Insulin requirement			
Group 1	54	17	31·5
Group 2	32	23	71·9
Group 3	81	54	66·7
Group 4	43	17	39·5
Control			
Excellent	57	17	29·8
Good	70	18	25·6
Fair	35	11	31·4
Poor	35	19	54·3

TABLE IV. THE RELATION BETWEEN CONTROL, RACE AND RETINOPATHY

Control	*Europeans*			*Non-Europeans*		
	Total No.	*No. with retinop.*	*%*	*Total No.*	*No. with retinop.*	*%*
Excellent ..	45	11	24·4	12	6	50·0
Good ..	48	14	29·2	22	4	18·2
Fair ..	17	2	11·8	18	9	50·0
Poor ..	19	10	52·6	16	9	73·8

Note. In 4 non-Europeans the degree of control could not be assessed.

Discussion

The first point of interest is that the incidence of retinopathy is higher in the non-Europeans than in the Europeans. As already indicated, the non-Europeans include a relatively higher incidence of patients with diabetes of less than 10 years' duration and a higher proportion of patients under the age of 40 years. Furthermore, separate study shows that, regardless of duration of diabetes (Table V) or age, the incidence of retinopathy is higher in the non-European. If the two main races be studied separately in relation to age the percentage with retinopathy in each age group will be as follows:

European	*Non-European*
Group A: no instances	Group: A 16·7%
Group B: 11·1%	Group: B 18·2%
Group C: 23·4%	Group: C 38·9%
Group D: 37·3%	Group: D 53·6%

The sex differences in the two main racial groups may be of importance, and have been analysed in detail (Table VI). It is apparent that while the European males have a higher incidence of retinopathy than the non-European males, there is a higher incidence of this complication among the non-European females than among the European females. And the high incidence of retinopathy in the non-Europeans as well as the difference in the incidence between the sexes irrespective of race is very largely contributed by this female group. If Table II is examined it will be seen that whereas half the non-European males are under 40 years, only 1/5th of the non-European females fall into this category. It might be supposed that the relatively high proportion of non-European females over the age of 40 years might account for the sex difference in the race group. However, if the incidence of retinopathy among the non-Europeans over the age of 40 years be considered alone, a large difference in incidence can still be demonstrated, viz.: 21·4 and 52·0% respectively for males and females. It may be stated, there-

TABLE V. THE RELATION BETWEEN DURATION, RACE AND RETINOPATHY

Race	*Totals*		*Under 10 years*				*Over 10 years*			
	Race	*Retinop.*	*No.*	*% of race total*	*Retinop.*	*% of race under 10 yrs*	*No.*	*% of race total*	*Retinop.*	*% of race over 10 yrs.*
E	129	37	87	67·4	20	23·0	41	31·8	17	41·5
N-E ..	81	32	69	85·2	23	33·3	11	13·6	9	81·8
All races ..	210	69	156	74·3	43	27·4	52	24·7	26	50·0

TABLE VI. THE RELATION BETWEEN RETINOPATHY, RACE AND SEX

Race	*Totals*		*Males*		*Females*		*Ratio males to females*
	Race	*Retinop.*	*No.*	*Retinop.*	*No.*	*Retinop.*	
E	129	37 (21·7%)	40	11 (27·5%)	89	26 (29·2%)	44·9%
N-E	81	32 (39·5%)	21	4 (19·04%)	60	28 (46·7%)	35·0%
All races	210	69	61	15	149	54	

TABLE VII. THE RELATION BETWEEN RETINOPATHY, AGE AND DURATION

Age-groups	*Duration under 10 years*			*Duration over 10 years*		
	Totals	*Retinopathy*		*Totals*	*Retinopathy*	
		No.	*Percent*		*No.*	*Percent*
A	11	1	1/11	1	0	0
	(25)	(1)	(1/25)	(7)	(3)	(42·9%)
B	14	0	—	6	3	50%
C	65	18	27·7%	17	7	41·2%
	(131)	(42)	(32·1%)	(45)	(23)	(51·1%)
D	66	24	36·4%	28	16	57·1%
Total	156	43		52	26	

fore, that whilst non-European females include an unusually large proportion of patients aged 40 years and over, this does not convincingly account for the sex difference in the two races, nor for the difference in incidence between the non-European males and females.

Comments

1. The incidence of retinopathy rises with increasing age.
2. The incidence of retinopathy is higher in the non-European than in the European. This is probably not influenced by age or duration of diabetes but may be associated with poorer control and a large proportion of females in the non-European group. These two features tend to weaken the case for a true racial difference, but suggest a difference in the behaviour of the sexes in the two races.
3. A high incidence of retinopathy in the non-European females compared with European females is not explained by age selection. It appears to account for the racial bias in the group as a whole as well as the difference between the two sexes irrespective of race.
4. If the 'poor' control group is separated from the other groups and the latter are considered together, analysis reveals a very significant difference between the 'poor' control group and the remainder in respect of the incidence of retinopathy, the incidence being higher in the 'poor' control group.
5. No correlation exists between insulin requirement and the incidence of retinopathy.
6. The high incidence in those with diabetes of long duration requires comment, particularly in relation to age selection. The situation is analysed in Table VII, and it is apparent that if the 'duration' groups are considered separately the proportion of patients in age-groups C and D is not very different in the two 'duration' groups, and the incidence of retinopathy rises with age, independent of duration. Among the small number in the younger age-group (A and B) it is interesting to note that of the 7 patients in the over-10-year duration group, 3 (42·9%) had retinopathy, whereas only 1 (4%) of the 25 patients in the under-10-year duration group, developed this complication. All this suggests that both age and duration of diabetes favour the development of retinopathy.

CARDIOVASCULAR COMPLICATIONS

Coronary artery disease was diagnosed in the presence of one or more of 4 features:

1. A history of angina pectoris or cardiac infarction with or without an associated electrocardiographic abnormality at the time of follow-up:

A history of cardiac infarction was obtained in 10 patients, 7 of whom subsequently experienced angina pectoris. In all but one of these there was ECG evidence of ischaemic damage and in this patient the history was acceptable beyond reasonable doubt.

Thirteen patients had angina pectoris only. Of these an ECG was normal in 4, compatible with ischaemia in the remaining 9.

Care was taken to exclude the less usual causes of angina pectoris such as cardiovascular syphilis, severe aortic stenosis, and anaemia.

2. Unequivocal ECG changes of infarction in the absence of a history of ischaemic pain:

Eight patients came into this category. The ECG of 6 additional patients were suggestive of posterior infarction but were possibly within normal limits. These were excluded from the group under discussion.

3. ECG changes suggesting ischaemic damage, i.e. abnormal ST segments and/or T waves, when clinical evidence for an alternative explanation (ventricular hypertrophy, digitalis effect, electrolyte disturbance, etc.) did not exist.

4. Two patients showed left bundle-branch block in the absence of symptoms of heart disease. One was moderately hypertensive, the other was a normotensive European male with symptoms and signs of peripheral vascular disease. These two patients are included in the group with coronary artery disease.

In 45 (21·4% of the total 210) patients these criteria for coronary artery disease were satisfied. They comprised 29 Europeans and 16 non-Europeans (10 Cape Coloured and 6 Malays). This represents an incidence of 22·5% and 19·8% in the two main racial groups.

Sixteen of the patients were male (26·2% of all the males in the series), 29 female (19·9% of all the females).

The age distribution was as follows:

0–19 years	nil
20–39 years	1
40–49 years	6
50–59 years	6
60 and over	32

The incidence in relation to duration of diabetes, insulin requirement and control is tabulated in Table VIII. Unfortunately we have no control series of non-diabetics with

which to compare the incidence of ischaemic heart disease in the cases under review.*

TABLE VIII. THE RELATION BETWEEN CORONARY ARTERY DISEASE, DURATION OF DIABETES, INSULIN REQUIREMENT AND CONTROL

	Total No.	No. with cor. art. dis.	% with cor. art. dis.
Duration of diabetes			
Under 10 years	156	29	12·1
10 years or longer	52	16	30·8
Insulin requirement			
Group 1	54	11	20·4
Group 2	32	10	31·3
Group 3	81	19	23·9
Group 4	43	5	11·6
Control			
Excellent	57	13	22·8
Good	70	18	25·7
Fair	35	6	17·1
Poor	35	8	22·9

Comment

It is found that the incidence of ischaemic heart disease is similar in the two racial groups and in the two sexes. It rises considerably in the older age-group and this may explain the higher incidence in those with diabetes of longer than 10 years' duration.

Some of these features are at variance with certain series in the literature. For example, Warren and Le Compte[10] found that 40% of diabetics have clinical or ECG evidence of coronary artery disease and, of these, 25% are under the age of 40 years.

No correlation appears to exist between the incidence of ischaemic heart disease and insulin requirement or diabetic control.

NEUROLOGICAL COMPLICATIONS

Although specific interrogation included all those complications of diabetes which are believed to have a neurological basis, the emphasis of this analysis will fall on the features that allow objective clinical assessment, which for the most part occur in the lower limbs. In order to separate this group of signs from the other forms of neuropathy it was decided to divide the material into 3 categories as follows:

Group 1. Cases presenting certain common objective criteria in the lower limbs.

Group 2. Cases with leg pain other than intermittent claudication.

Group 3. Other instances of neuropathy not classifiable in Groups 1 and 2.

Group 1

This group provides the corner-stone of this analysis. To qualify for this group there had to be present at least one of the following objective abnormalities:

1. Paresis or paralysis of the lower-motor-neurone type.
2. Tender calves.
3. Absent knee jerk with or without absent ankle jerk.
4. Absent ankle jerk.
5. Grossly diminished or absent vibration sense.

Only those tendon reflexes which were absent after reinforcement were included. Naturally, where these signs had an obvious alternative aetiology they were excluded from the totals.

The material was analysed in respect of incidence, duration, insulin requirement, control, sex, race, age, and in relation to leg pain and evidence of vascular disease.

Total incidence. Of the total of 210 patients in this series, 49 patients exhibited at least one of the above signs, an incidence of 23·3%. In 16 of the 49 patients, more than one of the signs was present, an incidence of 7·6%. The incidence of individual abnormalities within this group was as follows:

1. Paresis of the lower-motor-neurone type—no instances significant to the present survey were found.
2. Tender calves—10 instances, 4·8% of the total in this study.
3. Absent knee jerk—11 instances, 5·2% of the total.
4. Absent ankle jerk—29 instances, 13·8% of the total.
5. Diminished vibration sense—23 instances, 11·0% of the total.

Sex. There were 9 males and 40 females in this group, giving a percentage of the total number of each sex in the series of 14·7% and 27·2% respectively.

Insulin requirement and control. The distribution in respect of these features is shown in Table IX.

TABLE IX. THE RELATION BETWEEN GROUP-1 SIGNS, INSULIN REQUIREMENTS AND CONTROL

	Total in series	No. with group-1 signs	Percent. with group-1 signs
Insulin requirement			
Group 1	54	10	18·5
Group 2	32	5	15·6
Group 3	81	24	29·6
Group 4	43	10	23·2
Control			
Excellent	57	10	17·5
Good	70	16	22·8
Fair	35	7	20·0
Poor	35	14	40·0

Note. In 2 instances the degree of control could not be assessed.

Race. Separate consideration of the two main racial groups reveals that 29 Europeans (22·5% of the Europeans) and 20 non-Europeans (24·7% of the non-Europeans) showed evidence of group-1 neuropathy.

Age. Instances of group-1 neuropathy were distributed among the four age-groups defined earlier as follows:

No instances in age-group A (of 12 patients in this group)
1 in age-group B (of 20 patients in this group)
14 in age-group C (16·8% of the 83 patients in this group)
34 in age-group D (35·8% of the 95 patients in this group)

Because of the obvious relationship between age and duration, the distribution as regards duration in group-C (patients aged 40-59 years) and group-D (those aged 60 years and over) are given (see Table II). Group-C patients with diabetes of 10 or more years duration (17 patients) yielded 3 instances of group-1 neuropathy, an incidence of 17·6%; group-D patients with diabetes of the same duration (28 patients) yielded 9 instances of neuropathy, an incidence of 32·1%. Group-C patients with diabetes

* Dr. B. Bronte-Stewart has kindly made available to us figures from a survey of ischaemic heart disease in the general population in Cape Town. The only group strictly comparable to our own are males (equal numbers of European and Coloured) in the age-group 40-59. The incidence found here was 5·9% (in 239 subjects), which, even though it may tend to underestimate the true frequency, is still very much under the 14·5% shown by our diabetics in this age group. The approximately doubled likelihood of heart disease in diabetics is in accordance with the literature in general.

TABLE X. RELATION BETWEEN NEUROPATHY AND DURATION OF DIABETES

Duration (years)	*Total in series*	*Group-1 Neurop.*		*Group-2 Neurop.*		*Groups 1 and 2 combined*	
		No.	%	*No.*	%	*No.*	%
0– 4	100	18	18·0	13	13·0	31	31·0
5– 9	56	18	32·1	3	5·4	21	37·0
10–14	31	7	22·6	3	9·7	10	32·2
15 + ...	21	6	28·6	3	14·3	9	42·8
	208	49		22		71	

Note. In 2 instances duration was not assessed.

of less than 10 years duration (65 patients) yielded 11 instances of neuropathy, an incidence of 16·9%; group-D patients with diabetes of the same duration (66 patients) yielded 25 instances of neuropathy, an incidence of 37·9%. An increasing incidence of this complication was demonstrable, therefore, regardless of duration. As can be seen in Table II there are quite significant differences in the duration make-up of age-groups C and D, the percentage ratios (longer duration over shorter duration) for these two age-groups being 26·2% and 42·4%.

The incidence of neuropathy in relation to the duration of diabetes is shown in Table X. If the 'duration' groups are combined into 'under 10 years' and 'over 10 years' it will be seen that there were 36 patients with group-1 signs who had had their diabetes for less than 10 years—23·0% of the total number of diabetics in this category—and 13 patients who had had their diabetes for 10 years or more—25·0% of the total in this category.

Group 2

Under this heading are included the several varieties of leg pain, other than intermittent claudication, commonly met with in diabetic subjects. Obviously the assessment of such a symptom presents many difficulties; nevertheless an effort was made to include only genuine instances.

The only points of interest were the incidence of this symptom and its relationship to objective evidence of neuropathy and evidence of vascular disease.

Of the total number of patients only 22 complained of leg pain as defined above, an incidence of 10·5%. In 8 of these patients there were present one or more of the signs included in group 1 (36·4% of the patients with leg pain). Thus, 16·3% of the patients in group 1 had leg pain while the remaining 161 patients in this series yielded only 14 instances of this symptom, an incidence of 8·7%.

Seven patients, or 31·8% of those with leg pain showed evidence of vascular disease in the legs. As will be seen later, there were 48 patients in whom there was evidence of vascular disease in the legs. This gives an incidence of leg pain amongst these patients of 14·6%, as opposed to the incidence of 9·3% among those patients in whom there was no evidence of vascular disease. In 13 of the 22 patients with leg pain there was evidence of either neurological or vascular disease or both, an incidence of 59·1%.

Peripheral vascular disease in relation to neuropathy. Evidence of vascular disease in the lower limbs was sought in each patient on clinical grounds according to whether one or more of the following features were present: Intermittent claudication; absent pulsation in the posterior tibial, dorsalis pedis or other arteries of the lower limbs; amputation because of vascular disease; gangrene; or other obvious signs such as temperature or trophic changes attributable to vascular disease. Vascular disease was present in 48 patients, giving a total incidence of 22·9% for the series. In group 1, 18 patients (36·7% of this group) showed evidence of vascular disease. 37·5% of patients with vascular disease had group-1 signs. Therefore, in 30 patients, or 62·5% of those who had vascular disease, group-1 signs were absent. The 18 patients who presented signs of vascular disease and group-1 neuropathy constituted 8·6% of the total number of patients in this study. 27 Europeans, or 20·9% of the Europeans, and 21 non-Europeans, or 25·9% of the non-Europeans, presented evidence of vascular disease.

Group 3

This group embraces a miscellaneous collection of neurological features not classifiable under groups 1 and 2. Altogether there were 12 instances in this group, 8 of which were associated with group-1 signs, the remaining 4 being present as isolated neurological features.

The majority of examples in this group were instances of sensory disturbance—arm pain, paraesthesiae, superficial sensory loss, etc. There were 2 instances of disturbed bladder function and 1 of external rectus paresis. There were no instances of nocturnal diarrhoea, myelopathy, impotence, or pupillary disturbance.

Discussion

The subject of neuropathy has been adequately reviewed elsewhere.[6,9,7,5,1] It is not proposed, therefore, to review the subject, but merely to draw certain comparisons between our results and those reported in a few major contributions.

Because of the relatively small size of this series of patients it was not possible to draw many conclusions which could be statistically supported or were worth detailed analysis. Nevertheless, a number of trends were demonstrable, some of which are probably highly significant.

Assessment of the *total incidence* of neurological complications attributable to diabetes immediately raises a host of difficulties, each of which adds to the inaccuracy of the figures produced. These difficulties include: Differences in definition, the temporary nature of many features, and the validity of certain symptoms in persons who receive a painful daily reminder that they are abnormal; the problem of isolated neurological deficits, as for instance the absent ankle jerk or diminished vibration sense in relation to advancing age, not to speak of the degree of abnormality which is acceptable (for instance whether a tendon reflex is described as absent or merely diminished); the question whether diabetes is the cause of a neurological sign in a particular instance; and, finally, the limits of what is regarded

as primarily neurological as opposed to primarily vascular.

However, it would appear that the figure of 23·3% for certain common signs in the lower limb or 31·9% for all forms of neuropathy, both subjective and objective, arrived at in this survey is well within the wide range suggested by Bailey.[1] In his review Bailey found that, if all forms of neuropathy were included, the clinical incidence appeared to be approximately 50%, whereas he estimated that clinically significant diabetic neuropathy was probably less than 5%. Indeed, the incidence given by various workers has differed much more widely than this.[1,5]

Turning to a consideration of the *group*-1 signs, i.e. certain common signs occurring primarily in the lower limb, it is possible to make the following remarks. Of the *individual defects* the absent ankle jerk and loss of vibration sense were by far the commonest signs elicited. These had an incidence of 13·8% and 11·0% respectively of the total number of patients in the series, or 59·2% and 46·9% of the 49 cases in group 1.

It is generally agreed that absent deep tendon reflexes and diminished vibration sense are the commonest signs of diabetic neuropathy.[5,3,4,9,2] Reports in the literature give a variety of results for the incidence of these signs in the general diabetic population and for the relative incidence of these signs in groups of people showing evidence of neuropathy. Amongst their diabetic subjects Goodman *et al.*[5] found the ankle jerk to be absent in 48·2% and the knee jerk in 25·6% of subjects; amongst his 125 cases of diabetic neuropathy, Rundles[9] found that 81·0% had absent ankle jerks and 56·0% had absent knee jerks. The approach of different workers to these signs has varied. This is best illustrated by the wide differences which exist in the reports of diminished or absent vibration sense. There is general agreement that impaired vibration sensibility is the earliest and often the only sign of diabetic peripheral neuropathy. In Rundles' series of 125 cases with diabetic neuropathy, vibration sense was diminished or absent in 45·6%, a point of agreement between our study and his inasmuch as he found gross involvement of vibration sense to be less common than loss of tendon reflexes in the lower limbs. We feel that obvious impairment of vibration perception as tested by ordinary clinical methods is of some value in the estimation of what Bailey[1] has termed 'clinically significant diabetic neuropathy'. The probable exaggeration of its incidence as a result of non-specific factors, particularly age, should, however, be clearly appreciated.

Although at first glance there appeared to be a striking *sex difference* with respect to group-1 signs, an incidence of 26·8% and 14·7% respectively of the totals for female and male, more detailed analysis in relation to age (see Table II) and control revealed significant differences in the distribution of these two factors, particularly age, in the two sex groups. Separate consideration of the two sexes in respect of the two broad age-groups under and over 40 years demonstrated that age selection had some influence on the incidence in the two sexes in this analysis, the difference being due in certain measure to the significantly higher proportion of males in the younger age-group.

The table (Table IX) dealing with the occurrence of group-1 signs in respect of *duration, insulin requirement* and *control* details some interesting trends. Duration, if considered in two large groups—under 10 years and 10 years or longer—did not effect the incidence of these complications. When this analysis was carried further, into 5-year groups (see Table X) the effect of duration was still not dramatic, although some influence was demonstrable. The picture varied according to whether groups 1 and 2 were considered separately or combined. Of some interest was the relatively high incidence of neuropathy in the under-5-year group as well as the relative frequency of leg pain at the two extremes of duration of our study.

Insulin requirement did not influence the incidence of group-1 signs and in this respect our findings are in agreement with those of Jordan[6] as applied to his 'neuritic' group.

Analysis of control, however, provided an interesting result as seen elsewhere in this paper in relation to retinopathy. If the incidence in the 'poor' control group is contrasted with the incidence in the remaining 3 groups combined there results a highly significant difference between the two groups, there being a far higher liability to group-1 signs in the poorly controlled diabetic in our series. In case this reflected some gross difference in chance selection of other possibly influential factors the distribution of such factors as age, duration and sex was analysed; these features were found to be roughly comparable in the two groups.

Most authors would agree that whereas control is strongly correlated with the development of neuropathy[5,7,4] yet 'it is likely that neither the amount of dextrose in the blood nor the acetone and diacetic acid are the actual toxic agents in producing neuropathy'.[5]

Whilst it is well known that there is a variable relationship between duration of diabetes and the onset of neuropathy, there being instances in which symptoms have ante-dated the diabetes,[6,1] it is generally agreed that a period of somewhat over 5 years,[7,6,9,1] or longer,[2] usually precedes the onset of neurological features and that there is clear indication of the importance of duration.[5]

With regard to *race*, this survey showed no significant difference in liability to neurological complications between the two main racial groups, i.e. European and non-European.

Age appeared to exert considerable influence on the incidence of this limited group of neurological signs inasmuch as the incidence in the oldest group (group D) was twice that in the next group (group C). Numbers in the younger groups were too small to enable any comparison with these, although it is possibly worth mentioning that only one case was found under the age of 40 years.

Leg pain, as defined here, was revealed to be less frequent than anticipated if the incidence of 10·5% in this study is compared with the incidence derived from other sources. Often this feature is referred to by writers as 'the commonest symptom' of diabetic neuropathy without further attempt being made to derive its actual incidence among the diabetic population or to relate its incidence to the other features of diabetes. Where figures for pain in the extremities have been given they have varied from 5% to 49%, most authors giving an incidence above 10%.[5] As might be expected, analysis of the interrelationship between leg pain, neurological disorder in the legs, and signs of vascular insufficiency, underlined the alliance between these three aspects, not that any confirmation of an aetiological relationship can be assumed from these facts. Roughly one-third, or 36·4% of the patients with leg pain had one or more of the group-1 neurological signs, and roughly one-third, or 31·8%, pre-

sented signs of vascular insufficiency. If, however, the incidence of these three factors is combined, it can be shown that over one-half, or 59·1%, of patients with leg pain will have either neurological or vascular disorder, or both. Looking at this situation from another point of view, the incidence of leg pain among those patients with group-1 signs and among those with vascular disorder was roughly double that in the remainder of the patients under investigation. Despite these relationships, the large number of instances of leg pain unexplained on clinical grounds by the coexistence of neurological or vascular disorders enhances, at least in some measure, the probability of a functional metabolic mechanism in many cases.

Study of the *relationship between group-1 neurological signs and vascular disease* suggested a certain parallel between the development of these two disorders. The incidence of neurological disorder in the vascular group (37·5%) and the incidence of vascular insufficiency in group-1 (36·7%) were both significantly higher than the incidence of the corresponding disorders in the total of our patients, 23·3% and 22·9% respectively for the neurological and vascular groups.

No racial differences were detected in the incidence of vascular insufficiency in the lower limbs.

The alliance between these two disorders is probably largely conditioned by the fact that both have their maximum incidence in the older diabetics. It should be stressed that well over half of the group-1 patients had no evidence of vascular disease, and therefore, whatever the aetiological relationship between the two from a histological point of view, clinical support for such contentions would appear far from established in many, if not most, instances of diabetic neuropathy.

Evidence of occlusive peripheral vascular disease in diabetic subjects appears to vary widely. Examples of the incidence of occlusive vascular disease among diabetics given in the literature are 46·1%[5] and 37·0%.[8] As to the overlap between neuropathy and occlusive vascular disease Goodman *et al.*[5] in two groups of cases found the incidence of peripheral disease among those diabetics with neuropathy to vary from 36·4% to 54·7%, thereby leading that group of workers to the conclusion that whereas there was an obvious relationship between the two disorders the correlation was not yet sufficiently strong to establish a definite aetiological role.

Comment

The total incidence of neurological disorders arrived at in this study agrees with that group of authors who have made rather more conservative claims for the incidence of these complications. This fact has resulted partly from the use of simple clinical methods only, from obedience to unequivocal criteria, and from the fact that this study was confined to out-patients. It is felt that this approach, being widely applicable, has given results which will be of use for comparative purposes in large-scale investigations. Moreover, it allows possibly a closer estimate of what may be termed 'clinically significant' diabetic neuropathy.

Of the various aspects which were investigated, the most significant influences appeared to be increasing age and poor control. Our results demonstrate a parallel between clinically evident vascular insufficiency and neurological signs in the lower limbs, although most instances of neuropathy were not involved in this relationship.

Of the individual signs in the lower limbs, absent ankle jerks and diminished vibration sense were found more commonly than other signs. These two signs were found more commonly than objective evidence of significant superficial sensory loss.

There was some alliance between leg pain, as defined, and the presence of neurological and vascular disease, but in a large number of patients the occurrence of pain was not accompanied by clinically detectable organic disease.

CONCLUSIONS AND SUMMARY

The retinal, cardiovascular and neurological abnormalities occurring in 210 consecutively examined diabetic out-patients have been analysed. The patients are of mixed racial origins, and include white 'Europeans', Cape Coloured subjects, Cape Malays and Bantu. The incidence of clinically apparent renal disease was too small for analysis.

In general, all these 'complications' showed a tendency to increase with age; as regards duration of the diabetes, the neuropathy showed no such trend, while the incidence of vascular disorders did increase. There was no correlation between insulin dosage and incidence of complications, but most interesting was the finding of a significantly higher rate of retinopathy and of neuropathy in the 'poor control' group, whilst in cardiovascular disease the control of the diabetes appeared to play no part.

'White' and 'non-White' diabetics showed little or no difference in the incidence of the complications under discussion, except that retinopathy was unexpectedly frequent in Coloured females, even allowing for the higher proportion of these patients in the 'poor control' group. It must be realized that the pure Native (Bantu) diabetics were not considered separately, and none of this discussion applies to them as a race.

We should like to thank all others who were associated in this survey, including particularly Prof. G. C. Linder, Dr. Anne Linder, Dr. V. Schrire, Mr. John Daragh (statistician), Miss M. Rom (typist), and the ophthalmologists. The Medical Superintendent of Groote Schuur Hospital and Prof. J. F. Brock encouraged its inception and continuation, and Prof. F. Forman commented upon the manuscript. Finally, we acknowledge the financial assistance of the Council for Scientific and Industrial Research by grants to the Endocrine Research Group.

Note. Full statistical analysis has not been included, but is available on request from Dr. E. A. Allen.

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