AUTONOMIC NEUROPATHY AND IMPOTENCE IN ZAMBIAN DIABETICS

BY

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A DISSERTATION SUBMITTED TO THE UNIVERSITY OF ZAMBIA IN PARTIAL FULFILLMENT OF THE REQUIREMENT OF THE DEGREE OF MASTER OF MEDICINE

THE UNIVERSITY OF ZAMBIA

LUSAKA

1987

APPROVAL

This dissertation of CHISHIMBA MUKONDE LUMBWE is approved as fulfilling part of the requirements for the award of the Master of Medicine Degree by the University of Zambia.

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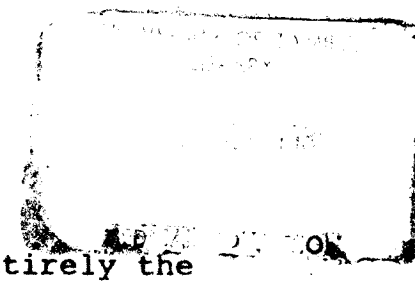
ACKNOWLEDGEMENTS

I would like to thank the following for the assistance they gave me during the preparation of this dissertation; Dr. Wadhawan my head of department for his advice and encouragement, Professor Bagshawe for her valuable suggestions and Dr. B. Nkowane for his help in the statistical analysis of the data.

I would also like to thank Mrs. C. Zulu and Mrs. M. Miyanda my two assistants on the electrocardiograph and Mrs. M. Kamushila for her secretarial help. Thanks are also due to the patients and controls who made this study possible and to my wife and children for their patience.



DECLARATION

I hereby certify that this Study is entirely the result of my individual effort. The various sources to which I am indebted have been acknowledged in the bibliography. I also declare that the work presented in this study for the degree of Master of Medicine (M.Med) has not been presented either wholly or in part for any other degree and is not currently being submitted for any other degree.

ABSTRACT

A study was carried out among male diabetic subjects over a period of six months to determine the prevalences of both autonomic neuropathy and impotence in diabetics in Zambia. The subjects of the study group were from those diabetics attending the diabetic outpatient clinic at the University Teaching Hospital, Lusaka, Zambia. Three tests were used to diagnose autonomic neuropathy;

1. A fall in systolic blood pressure of more than 30 mmHg from supine to erect.

2. An abnormal heart rate response to standing measured on an electro cardiogram.

3. An abnormal heart rate response to deep breathing, measured on an electro cardiogram, expressed as Expiratory : Inspiratory (E:1) ratio. The normal E:1 ratios had previously been determined in healthy male Zambians.

Autonomic neuropathy was considered to be present if any one of the above tests were abnormal.

Out of a total of forty two diabetic subjects admitted to the study fifteen (35.7%) had autonomic neuropathy; impotence was present in fourteen subjects (33.3%). The prevalence of autonomic neuropathy in impotent diabetics was 64.3%.

These findings are comparable to results done elsewhere. As symptomatic autonomic neuropathy carries a grave prognosis, this complication should be kept in mind and looked for in all diabetic patients.

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CHAPTER I : AIM OF THE STUDY

AIMS

The aims of this study were;

1. To determine the prevalence of autonomic neuropathy among male Zambian diabetics and it's relationship to age and duration of diabetes.

2. To determine the prevalence of impotence among the same group of diabetics.

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CHAPTER II : INTRODUCTION

INTRODUCTION

A. General

It's only during the last decade or so that the importance of autonomic neuropathy in diabetes mellitus has been appreciated and simple objective tests to confirm it's presence developed. Subclinical autonomic nerve damage is present more commonly than was previously suspected, and as its relationship to morbidity and mortality has become more apparent it has assumed greater significance. Many large series have found that twenty to forty percent of all diabetics have some form of autonomic dysfunction (Sharpey et al 1960; Ewing et al 1974; Hilsted et al 1979; Dryberg et al; 1981).

The natural history of autonomic damage in diabetes is still under study but it would seem that parasympathetic damage occurs first later sympathetic damage occurs (Ewing et al 1980; Ewing et al 1981). Little is known about the consequences of autonomic neuropathy in asymptomatic patients but autonomic neuropathy with symptoms carries a worse prognosis than any other complication of diabetes (Ewing et al 1980a). These patients show a high mortality (Ewing et al 1976). and cardiorespiratory arrest is a specific feature noted particularly during or after surgery when it is possibly related to the anaesthesia and also in patients given any drug which has a central respiratory

depressant action (Page et al 1978; Sundkvist 1981). With the simplified tests for autonomic neuropathy now employed (Vide infra) it has become imperative to assess autonomic function of any diabetic before surgery is contemplated, and after surgery intensive care should be mandatory where available. Solar (1975) and Bradley (1962) also mention a higher incidence of mortality from myocardial infarctions and the increased incidence of painless infarctions in diabetics with autonomic neuropathy.

B. Pathogenesis

A number of mechanisms have been cited as pathogenic in diabetic neuropathy.

Vascular factors - Fagerberg (1956) described endothelial thickening and progressive sclerosis of the vasa nervorum in sural nerve biopsies. Increased platelet aggregation (Kwamm et al 1972; H. Heath et al 1971) may also play a part as well as impaired fibrinolysis (Chakrabart et al; 1974; Fuller et al 1979). These mechanisms may play some role but evidence suggest that they are not solely responsible for the neuropathy (Ward et al 1971; Porte et al 1981).

Diabetes per ser - It has been postulated that axonal dwindling and loss of function occur in peripheral nerves of diabetics as part of the overall diabetic syndrome (Vracko et al 1974; Behse et al 1977).

Immune factors - Existing evidence strongly suggests an auto immune basis for insulin dependent diabetes mellitus and it is thought that neuropathy may be part of the immune syndrome.

Metabolic factors - In diabetic patients, abnormalities of carbohydrate and lipid metabolism in nerves have been described. Peripheral nerves of diabetic animal models have been shown to contain six times more glucose, twenty times more sorbitol and ten times more fructose than those of non diabetic animals (Stewart et al 1967; Gabbay et al 1966; Steward et al 1966; Ward et al 1972). There is also an accumulation of sorbitol from the polyol pathway and since neither sorbitol nor fructose diffuse easily they become trapped in the nerve cell causing intra cellular hypertonicity. The resultant osmotic effect is thought to cause cell damage. The other mechanism for nerve damage which has been postulated is that due to myo-inositol. Diabeties are known to excrete large amounts of myo-inositol in the urine (Clements et al 1974). Myo-inositol is important in maintaining the intergrity of the cell membrane. Myo-inositol is actively transported into cells and failure of this mechanism may predispose to neuropathy. It has been found that the peripheral nerves of diabetic animals contain only twenty percent of myo-inositol found in nerves of control animals (Stewart et al 1966; Green et al 1975). Supplements of myo-

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inositol in human diabetics have been reported to improve some forms of neuropathy (Clements et al 1977). It would thus seem that abnormalities in myo-inositol metabolism may play an important role in the pathogenesis of autonomic neuropathy.

C. Symptoms

The symptoms of autonomic neuropathy are varied and the disorder is usually chronic. The onset of symptoms is insiduous and they usually develop late in the disease. The majority of patients who experience symptoms of autonomic neuropathy also have clinical evidence of peripheral neuropathy. (Sundkvist et al 1979; Sive et al 1983; Sundkvist et al 1981).

Postural hypotension - Dizziness on standing is the most disabling symptom of autonomic damage but fortunately also probably the least common. (Ewing et al 1982). Postural hypotension has been defined as an immediate fall of more than 30 mmHg in the systolic blood pressure occuring on standing after lying down (Ewing et al 1976b). Some patients remain asymptomatic after this fall but the majority are symptomatic.

Sweating disturbances - Both anhidrosis and hyperhydrosis, may occur (Goodman et al 1966). Gustatory hyperhydrosis is however more frequent.

Gastric Symptoms - Gastric atony and retention may be found and patients may complain of having a bloated feeling.

Diarrhoea - The exact mechanism of diarrhoea is obscure. The typical picture is that of an explosive nocturnal diarrhoea and a few patients complain of faecal incontinence as opposed to diarrhoea.

Bladder dysfunction and urinary retention - This complication also occurs in autonomic neuropathy. The initial symptoms are those of an increasing bladder paralysis and urinary retention, later followed by difficulty in initiative micturition, poor stream and overflow incontinence.

Hypoglycaemic unawareness - The early symptoms of hypoglycaemia, that is palpitations, sweating, anxiety, hunger and tremor are mediated via the autonomic nervous system. Autonomic neuropathy may lead to loss of these warning symptoms and may result in sudden onset of neurological symptoms of confusion, decreased level of consciousness and coma.

Cardio pulmonary arrests - (vide supra).

Impotence - It is difficult to find a universally acceptable definition of impotence but for the purpose of this study the definition by Joel Charles (1971) was considered adequate; "Inability to initiate the sexual act to the satisfaction of both partners, independently of external circumstances, and to complete it with organism by ejaculation still proceeding in a state of erection". There are difficulties in trying

to differentiate organic from psychogenic impotence but table II.1 lists some of the differences to be looked for. Presence of nocturnal penile tumescence is the most important parameter but this requires some special equipment. The penis is comprised of fibro mascular stroma and erectile fissue. When the penis is flacid the erectile tissue is virtually free of blood. During erection penile blood flow increases while out flow decreases with resulting accumulation of blood in the vascular spaces. The drainage of blood in these vascular spaces is under the control of the parasympathetic nervous system through the nervi erigentes. The autonomic nervous system is thus very important in controlling erection and its dysfunction leads to impotence (Weiss et al 1972). Ejaculatory disturbances due to altered integrity of the internal bladder sphincter which is also dependent on the autonomic nervous system can also be encountered. About 40% of male diabetics have been found to have impotence by various workers (Sive et al 1983; Vink et al 1978; Faerman et al 1972; Kolodny et al 1974; Rubin et al 1958; Ellenberg et al 1971; Schoffling et al 1963; Rausch et al 1970).

However, the majority of patients do not volunteer this information about impotence which is usually elicited on direct questioning. The consequence of not diagnosing and defining the cause of impotence can be

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Table II.1

Features differentiating organic from Psychogenic Impotence.

Organic	Psychogenic
- Insiduous	- Acute onset, often related to specific event.
- Persistent and progressive not affected by partner	- May be variable May be influenced by partner
- Libido intact	- Libido variable
- Loss of morning erections and nocturnal tumescence	- Penile tumescence retained

serious. Impotence in the diabetic can be organic or psychogenic or a combination of both. In a few patients impotence may be a presenting symptom in which case its probably due to metabolic disturbance of uncontrolled diabetes and may disappear on establishing diabetic control. Vascular disease as a complication of diabetes may contribute to impotence (Simpson et al 1950; Abelson et al 1975).

Hormonal dysfunction was at one time considered a cause of diabetic impotence (Schoffling et al 1963; Distiller et al 1975) but several studies have been done which refute this (Faerman et al 1972; Kolodny et al 1974; Kent et al 1966; Wright et al 1976). Autonomic neuropathy is the single most important factor in diabetic impotence and is present in up to 70% of impotent diabetics (Vinik et al 1978; Ellenberg et al 1971; Jimenez et al 1977; Faerman et al 1974).

D. Diagnosis of autonomic neuropathy

There are several tests which have been developed to test the integrity of the autonomic nervous system. Some are complex and require computers while others are simple, reliable, reproducible and non-invasive.

Autonomic neuropathy can be suspected if there is loss of testicular sensation on physical examination (Campbell et al 1974). A resting tachycardia, pulse more than ninty beats per minute is suggestive of autonomic neuropathy. (See Table II.2 for some of the tests of autonomic neuropathy).

Table II.2 Common tests of autonomic function.

Tests of Parasympathetic Function	Normal	Borderline	Abnormal
Heart rate response to valsava manoeuvre	⩾1.21	1.11-1.20	⩽1.10
Heart rate (R-R) variation during deep breathing	1. *E:1 ratio depending on normal range for population 2. ⩾15 beat per min	11-14	⩽10
**Immediate heart rate response to standing (30:15 ratio)	>1.04	1.01-1.03	<1.00
Tests of sympathetic function			
BP response to standing (Systolic)	<10 mmHg	11-29	>30
BP response to sustained handgrip (Diastolic)	>16 mgHg	11-15	<10

* E:I = Expiration * Inspiration ratio

** See text for explanation

Table II.3 lists the other known but infrequently used tests of autonomic neuropathy.

I. TESTS REFLECTING CARDIAC PARASYMPATHETIC DAMAGE

1. Heart rate response to vasalva manouvre.

The standardized vasalva manouvre using an ECG to record the heart rate is easily performed at bed side. During the manouvre the heart rate goes up while the blood pressure falls. Afterwards the blood pressure rises over shooting it's resting value and the heart slows down. This response can be abolished by atropine and is not affected by propranolol suggesting that it is mediated by the vagus nerve (Ewing et al 1978). In patients with autonomic damage there is no change in heart rate and the blood pressure falls slowly during strain and return slowly afterwards with no overshoot rise.

2. Heart rate (R-R interval) variation during deep breathing.

This sinus arrythmia is normal and depends on an intact parasympathetic system. This variation is unaffected by propranolol, abolished by atropine, more pronounced at slower heart rates, during deep breathing and in younger subjects. (Ewing et al 1982; Smith et al 1981; Wielinget et al 1982).

Heart rate variation can be studied during quiet breathing, during a series of deep breaths or after a single deep breath, an ECG being used to record the heart rate. What has not been agreed on is whether a single deep breath or averaging six deep breaths in a minute is more reliable. There is evidence in support of both. (Mackay et al 1980; Bennet et al 1978; Ewing et al 1981). The results of this test are expressed as either the difference in heart rate in inspiration and expiration or as a ratio of the measured R-R interval in millimetres in expiration and inspiration, the E:1 ratio.

Again there's no consensus on which is better but a point to note here is that some authorities use fixed cut off points whereas it has been clearly shown that the cut-off point should depend on the age of the patient. (Sundkvist et al 1979; Ghareebs et al 1985; Ewing et al 1981).

Since this was one of the tests used in this study a preliminary study on normal Zambians, comparing the results using one, three and six deep breaths and the effect of age was carried out and detailed in the next Chapter.

3. Immediate Heart rate response to standing.

During the change from lying to standing an immediate increase in heart rate occurs at around the fifteen beat after standing followed by a relative brady-cardia at around the thirtieth beat. This response is

mediated by the vagus nerve (Ewing et al 1978; Ewing et al 1980). Diabetics with autonomic neuropathy show little on no change in heart rate. This test is simple and does not depend on age.

II. TESTS REFLECTINGHSYMPATHETIC DAMAGE

1. Blood pressure response to standing.

On standing a fall in blood pressure results due to the pooling of blood in the legs and this is rapidly corrected by vasoconstriction. The blood pressure falls on standing and remains lower than in the lying position in patients with autonomic neuropathy. Systolic pressure is important in this reflex. This test is abnormal only if sympathetic damage is severe.

2. Blood pressure response to sustained hand grip.

A sharp rise in blood pressure occurs in sustained hand grip. This is due to a heart rate dependent increase in cardiac output with unchanged peripheral resistance (Ewing et al 1978). Sympathetic nervous damage reduces the rise in the diastolic blood pressure.

E. OTHER TESTS

I. Pupillary responses to pharmacological agents like methacholine and adrenaline can also be used (Turner et al 1975). An easier test is to consider failure to dilate in darkness and failure to constrict to light as evidence of autonomic dysfunction (Ghareeb et al 1984; Smith et al 1978).

II. Invasive methods of assessing autonomic neuropathy have been described but are no longer used because of simpler tests available. These include estimation of gastric acid secretion in response to insulin hypoglycaemia, a measure of vagal function (Hollander et al 1946) and cystometrograms which correlate well with autonomic bladder function and impotence.

III. There are also a few biochemical tests like the plasma pancreatic polypeptide (PP) response to insulin hypoglycaemia (Levitt et al 1980).

IV. Peripheral nerve conduction velocities used to evaluate peripheral neuropathy is also delayed in the majority of patients with autonomic neuropathy.

Out of these battery of tests three were chosen, two of which measure parasympathetic function and one for sympathetic function. The tests where the heart rate (R-R interval) variation during deep breathing, immediate heart rate response to standing and the blood pressure reponse to standing. These tests are dealt with in detail in the next chapter.

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Other tests of autonomic junction.

TABLE II.3

TEST	RESULTS
Pupillary responses to Pharmacological agents and to light.	SLUGGISH
Estimation of gastric acid secretion in response to insulin hypoglycaemia.	POOR RESPONSE
Plasma pancreatic polypeptide response to insulin hypoglycaemia.	POOR RESPONSE
Peripheral nerve conduction velocity.	DELAYED

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CHAPTER III : METHODS AND MATERIALS

METHODS AND MATERIALS III

A. MATERIALS

1. Aneroid Sphygmomanometer
2. Electrocardiograph

B. METHOD

The study consisted of two main parts:

1. Construction of an age related normal range of *E:1* ratios for healthy Zambian males from heart rate variation during deep breathing.

2. Assessment of diabetic patients admitted to the study, using three tests:

   a) The heart rate (R-R interval) variation during deep breathing based on the constructed age related normal range.

   b) Immediate heart rate response to standing.

   c) Blood pressure response to standing.

1. Construction of age related normal range of E:1 ratios

Forty three healthy Zambian males who had passed at full medical examination at the medical examinations clinic of the University Teaching Hospital were tested to determine the normal range, and act as controls.

The mean age was 34.6±13.6 years and the range was 15 to 65 years.

Informed consent was obtained and with the subject supine and relaxed the electrocardiograph was connected. The technique was first demonstrated, deep breaths, six in a minute lasting approximately five seconds in and five seconds out. The recording was then started, and displayed in conventional form on paper run at speed 50 mm/s in lead II. A recording was taken with the subject breathing normally and, while the ECG recording continued, the subject was instructed when to breath in and out, a marker being used each time. The shortest R-R interval during inspiration (I) and the longest during expiration (E) were measured with a ruler and the E:I ratio calculated.

The E:I ratio was chosen to express the results instead of calculating the heart rate difference because this would give much more precision.

To determine whether it is better to calculate only the E:I ratio for one single deep breath or take the mean of several deep breaths, the E:I ratio was calculated in each case at the first deep breath, as a mean of the first three deep breaths and as a mean of the six deep breaths.

Figures III.I, III.2, III.3 and III.4 show the kind of electrocardiograms obtained and the E:I ratios calculated. For each of the three methods used to determine E:I ratios, that is using one deep breath, three deep breaths or six deep breaths, the E:I ratio

decreases significantly with age, with p equal to 0.00001, 0.00001 and 0.00008 respectively. To obtain a normal distribution of the ratios according to age simple linear regression was used to obtain the best fitting line for each of three methods with age as the predictor variable and the E:I ratio as the dependent variable. Figure III.5 is an example of the scatter diagram obtained when age was plotted against the E:I ratio and figure III.6 shows the line obtained as the best fit using simple linear regression and taking the mean of three deep breaths.

The following are the regression equations obtained using the E:I ratios of

a) one deep breath

$$Y = 1.802383 - (1.35097 \times 10^{-2}) * X$$

b) Three deep breaths

$$Y = 1.808883 - (1.350266 \times 10^{-2}) * X$$

c) Six deep breaths

$$Y = 1.780273 - (1.370698 \times 10^{-2}) * X$$

In each case X is the predictor variable age and Y is the dependent variable, the E:I ratio.

Then using the students T - Test

1) a and b, 2) a and c and 3) b and c were compared and found NOT to be significantly different with p equal to 0.8860822, 0.4557056 and 0.5501311 respectively.s This shows clearly that whether the E:I ratio is based on one deep breath, the mean of three deep breaths or the mean of six deep breaths, statistically the results will be the same. In this study the mean of 3 deep breaths was used to construct the age related normal range of E:I ratios, and in evaluating diabetic subjects.

A plot of the transformed ratios on age is linear allowing the 90th and 95th percentiles to be calculated (figure III.6). Ratios below the lower 95th percentile are abnormal that is subjects have autonomic neuropathy and thosebetween the 90th and 95th percentile are borderline. (Fischer et al 1970, Armitage et al 1971, Theodore et al 1974).

An important point to note here is that in Zambians of around sixty years of age and above, the E:I ratio is almost unity, 1.0. There is almost no variation in heart rate during deep inspiration, a point which has been noted by other workers (Sundkvist 1979).

The E:I ratios calculated from the electrocardiograms of diabetic patients were interpreted against the constructed normal range according to age.

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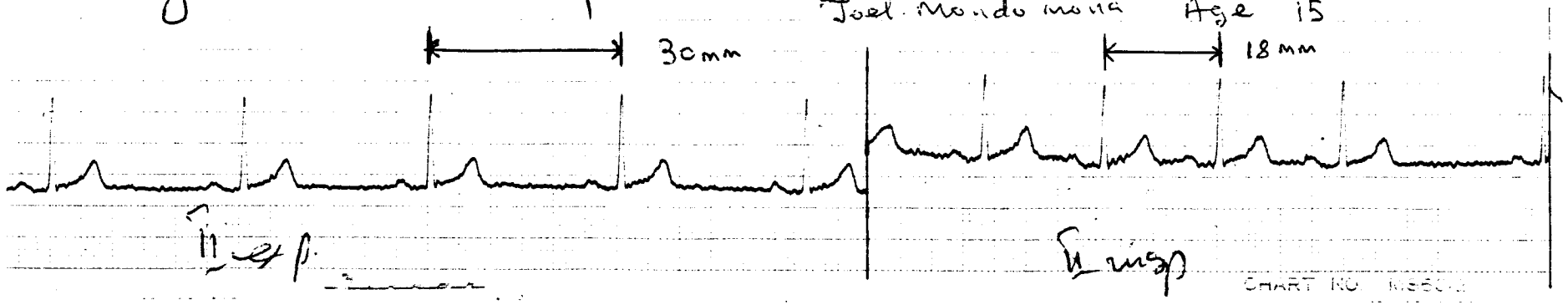
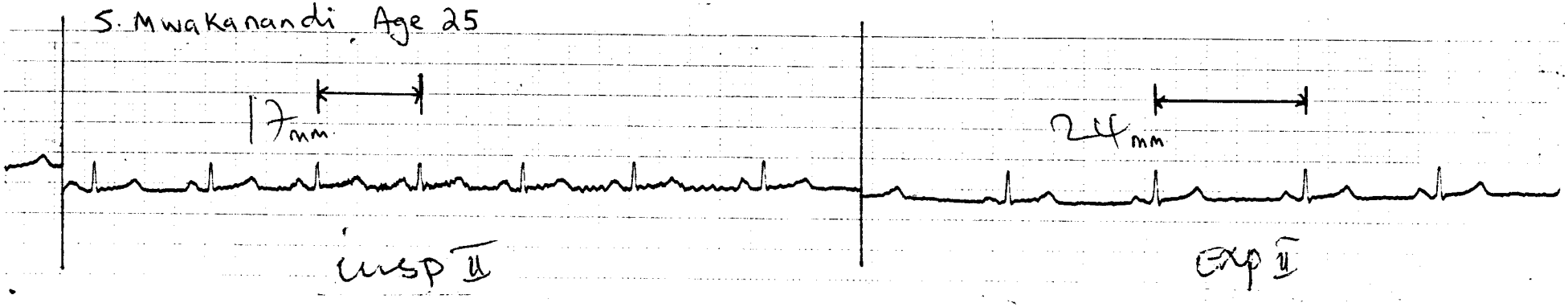


Figure III.2 Normal electrogram during deep breathing of a 25 year old Zambian E I ratio 1.41



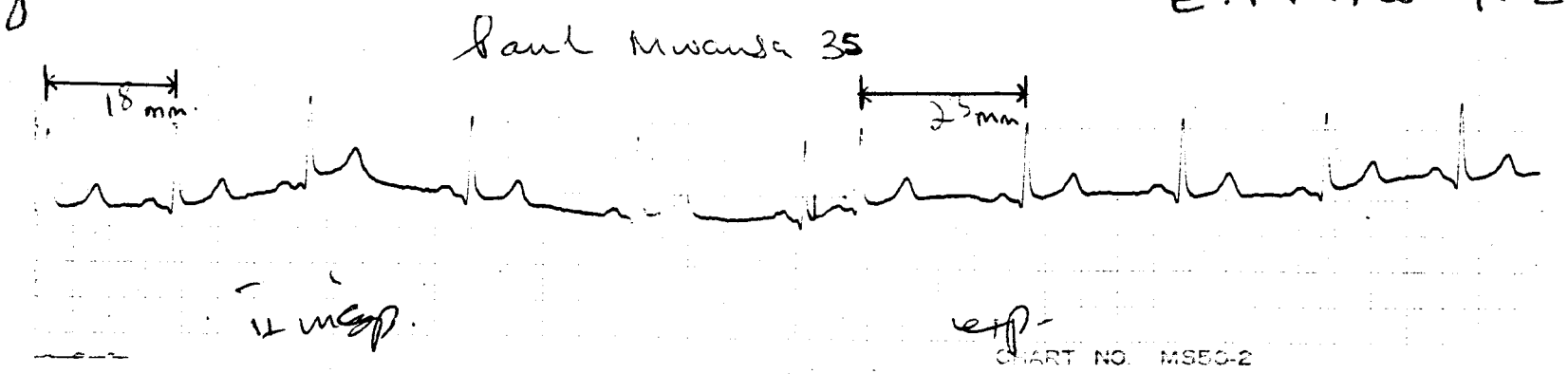


Figure III.4 Normal electrogram during deep breathing of a 55 year old Zambian E:I ratio 1.05

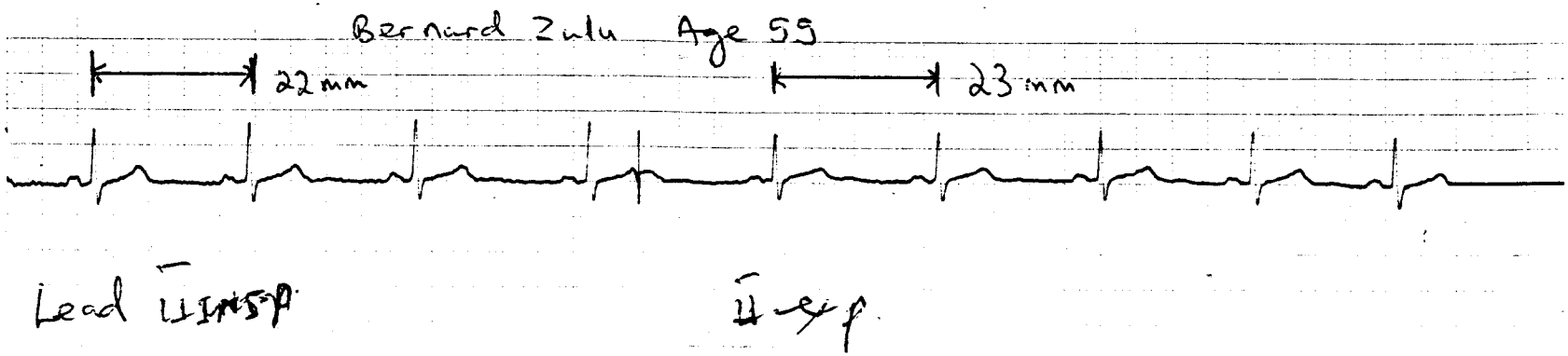


Figure 1. Scatter diagram of E:I ratios plotted against age

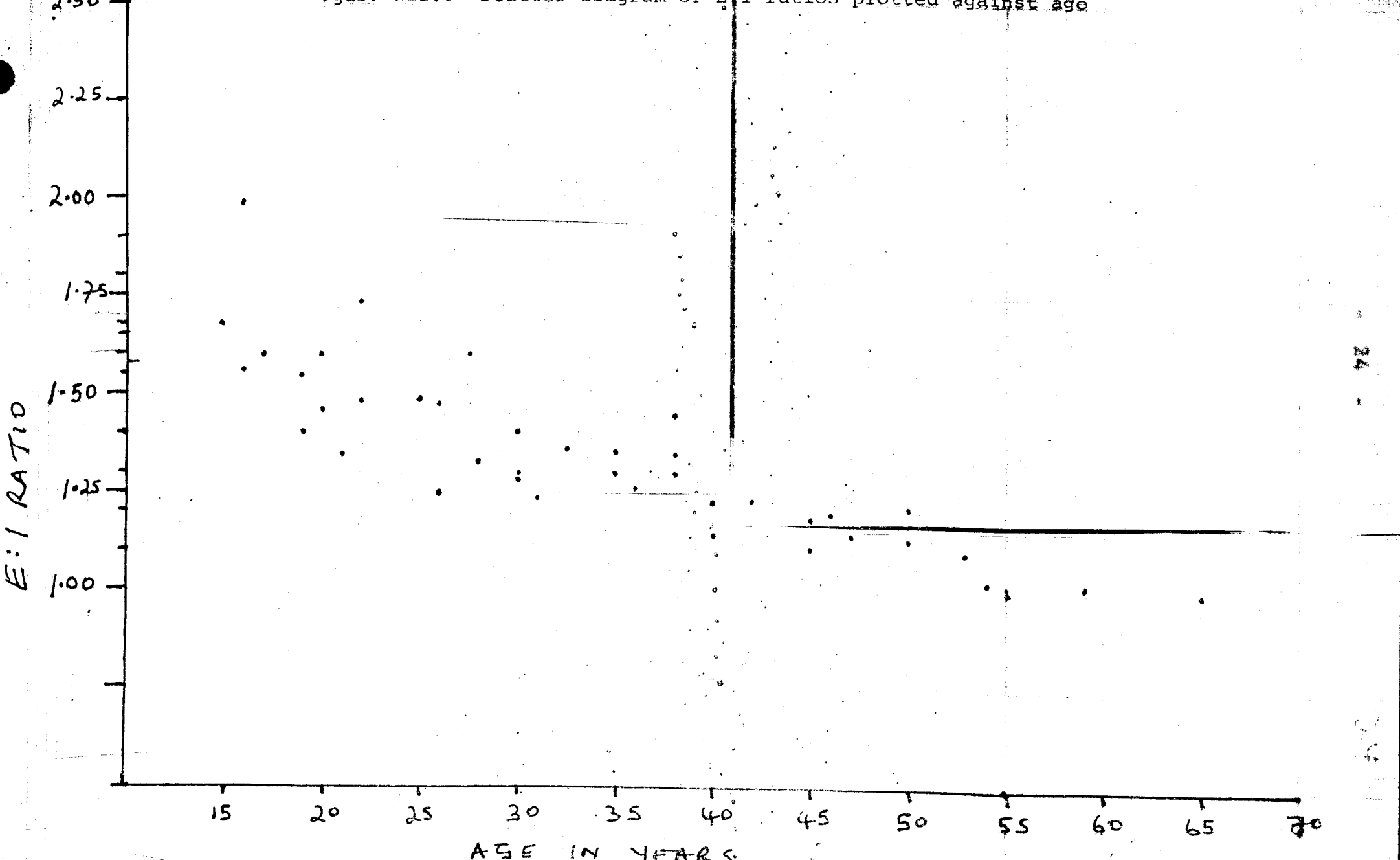


Figure III.6 Normal range of E:I ratios versus age by simple linear regression

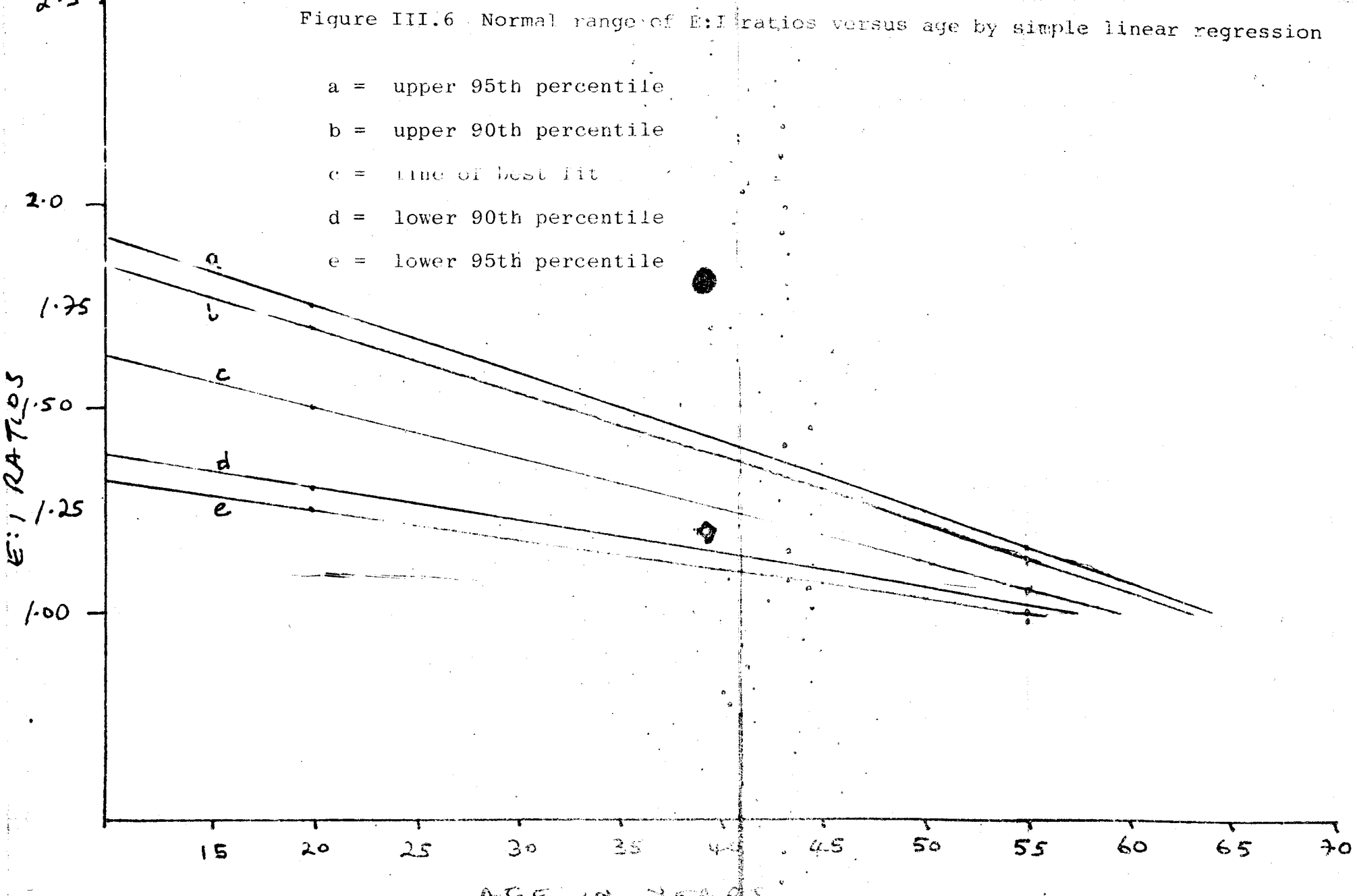
a = upper 95th percentile

b = upper 90th percentile

c = line of best fit

d = lower 90th percentile

e = lower 95th percentile



2. Assessment of diabetic patients admitted to the Study

Forty two Zambian diabetics attending the diabetic clinic were admitted to the study. Thirty were insulin dependent diabetics and twelve were non-insulin dependent diabetics the mean age being 38.6 ± 10 and range 19 - 57. The selection of subjects was randomized.

The admission criteria were:

a) Male, because of the need to look more into impotence.

b) Age, between fifteen and sixty years

c) Diabetes present for three years or longer

d) Willingness to take part in the study, consent being obtained in all cases.

The exclusion criteria were:

a) Presence of other major illnesses apart from diabetes like hypertension or heart disease.

b) The taking of any cardiotonic drugs or drugs known to have side effects like impotence for example methyldopa and also drugs acting on the autonomic nervous system like propantheline and propranolol.

On the first visit a questionnaire was completed in which a detailed history was taken especially with regard to symptoms of autonomic neuropathy and impotence.

The subjects were then examined and the blood pressure taken in supine and erect positions. Examination of the nervous system included ankle reflexes and vibration sense to determine presence of peripheral neuropathy, absent ankle reflexes and impared vibration sense were considered signs of peripheral neuropathy. During the same or subsequent visit the electrocardiogram was performed in deep inspiration and after five minutes rest period another tracing was taken to measure heart rate response to standing.

The point of starting to stand was marked on the electrocardiogram. This procedure was done in both controls and diabetic subjects.

The shortest R-R interval at around the 15th beat and the longest R-R interval at around the 30th beat were measured with a ruler in millimetres. The result was expressed as the 30:15 ratio. A ratio equal to or less than 1.00 is abnormal, between 1.01 and 1.03 is borderline and greater than or equal to 1.04 is normal.

Comparison of the means of the following variables, age, 30:15 ratio, resting heart rate, duration of diabetes in diabetics and controls, were done using the student's T-test for independent samples. A p-value equal to or less than 0.05 was sonsidered statistically significant.

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CHAPTER IV : RESULTS

RESULTS

Forty two diabetic subjects and forty three control subjects were studied. Thirty diabetic subjects had insulin dependent diabetes mellitus while twelve had non-insulin dependent diabetes mellitus. The subjects were considered to have autonomic neuropathy if any one of the three tests of autonomic function was abnormal.

1. Age

The mean age of the controls was 34.6 years. The mean age of all the diabetic subjects was 38.6 years. The mean age of the diabetic subjects with autonomic neuropathy was 38.5 years while that of the subjects without autonomic neuropathy was 38.6 years. Table IV.1 summarizes these which are given with their standard deviations. There was no statistical difference between these ages.

2. Duration of diabetes

The mean duration of diabetes in the whole study group was 8.7 years. The mean in diabetic subjects with autonomic neuropathy and in those without autonomic neuropathy was 8.6 years and 8.8 years respectively. There was no statistical difference between the figures (Table IV.1 and appendix).

3. Social habits

Nine subjects with autonomic neuropathy said they followed their diet strictly while six said they followed their prescribed diabetic diet only sometimes. In the group

11.6%. Overall among the diabetic subjects fourteen had impotence (figure IV.1).

5. Clinical examination

The mean resting heart rate in the controls was 72 beats per minute while in the diabetic subjects it was 74 beats per minute. In the diabetic subjects with autonomic neuropathy it was 77 beats per minute and in those without autonomic neuropathy it was 71 beats per minute. There is no statistical difference in these figures.

Seven subjects in the diabetic study group had evidence of peripheral neuropathy on examination, determined by impaired testicular sensation, impaired vibration sense and lack of ankle reflexes. Six of these seven subjects also had evidence of autonomic neuropathy. No one in the control group had evidence of peripheral neuropathy.

6. Tests of autonomic function

a) Deep breathing test - The results of the E:1 ratios were compared to the normal range contructed from the forty three controls as explained in the last chapter. Fourteen diabetic subjects showed an abnormal E:I ratio, two subjects had a borderline result and the remaining twenty six had a normal E:1 ratio.(Table IV.4).

Figures IV.2 and IV.3 are examples of the E:1 ratio from electrocardiogram tracings of two diabetic patients. Figure IV.2 shows an abnormal E:I ratio for a thirty eight

year old man. There's hardly any change in the R-R interval between inspiration and expiration. Figure IV.3 shows a normal E:I ratio for a thirty three year old man. The amplitude of the change between inspiration and expiration is evident.

b) Heart rate response to standing.

In the control subjects eight had a borderline 30:15 ratio while thirty two had a normal ratio. (Three of the tracings were not analyzed because of technical inaccuracies.)

Among the diabetic subjects, eleven had an abnormal 30:15 ratio, fifteen had a borderline ratio and sixteen had a normal ratio (Table IV.4). Figure IV.4, IV.5 and IV.6 are examples of the electrograms obtained. Figure IV.4 shows a normal 30:15 ratio of 1.07 while figure IV.5 shows a borderline ratio of 1.03 and figure IV.6 shows an abnormal 30:15 ratio of 0.89.

Table IV.1 gives the means and the standard deviations of the E:I ratios and the 30:15 ratios comparing control subjects with diabetic subjects with normal or borderline results of autonomic function and those with abnormal function.

c) Blood pressure response to standing.

Only one subject had an abnormal fall in systolic pressure on standing. The rest were within normal. In the control subjects there was no abnormal fall in blood pressure on standing in anyone.

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In the fourteen subjects with impotence among the diabetic subjects, nine had one abnormal test or more indicating presence of autonomic neuropathy. In the controls, the five subjects with impotence had normal autonomic function.

7. Statistical tests (Students T-test)

The means of the 30:15 ratios of the controls and the diabetics with autonomic neuropathy were tested for significance and found to be significantly different ($P = 0.0008$). The same 30:15 ratio in controls was again tested against the mean 30:15 ratio of diabetic subjects without autonomic neuropathy and found NOT to be significantly different ($P = 0.85$).

The mean resting heart rate for the three groups were also tested for significance and found NOT to be significant. Table IV.5 gives a summary of the means and their standard errors of various variable tested against the controls. Where there is any statistical difference there is a mark and an explanation at the bottom of the table.

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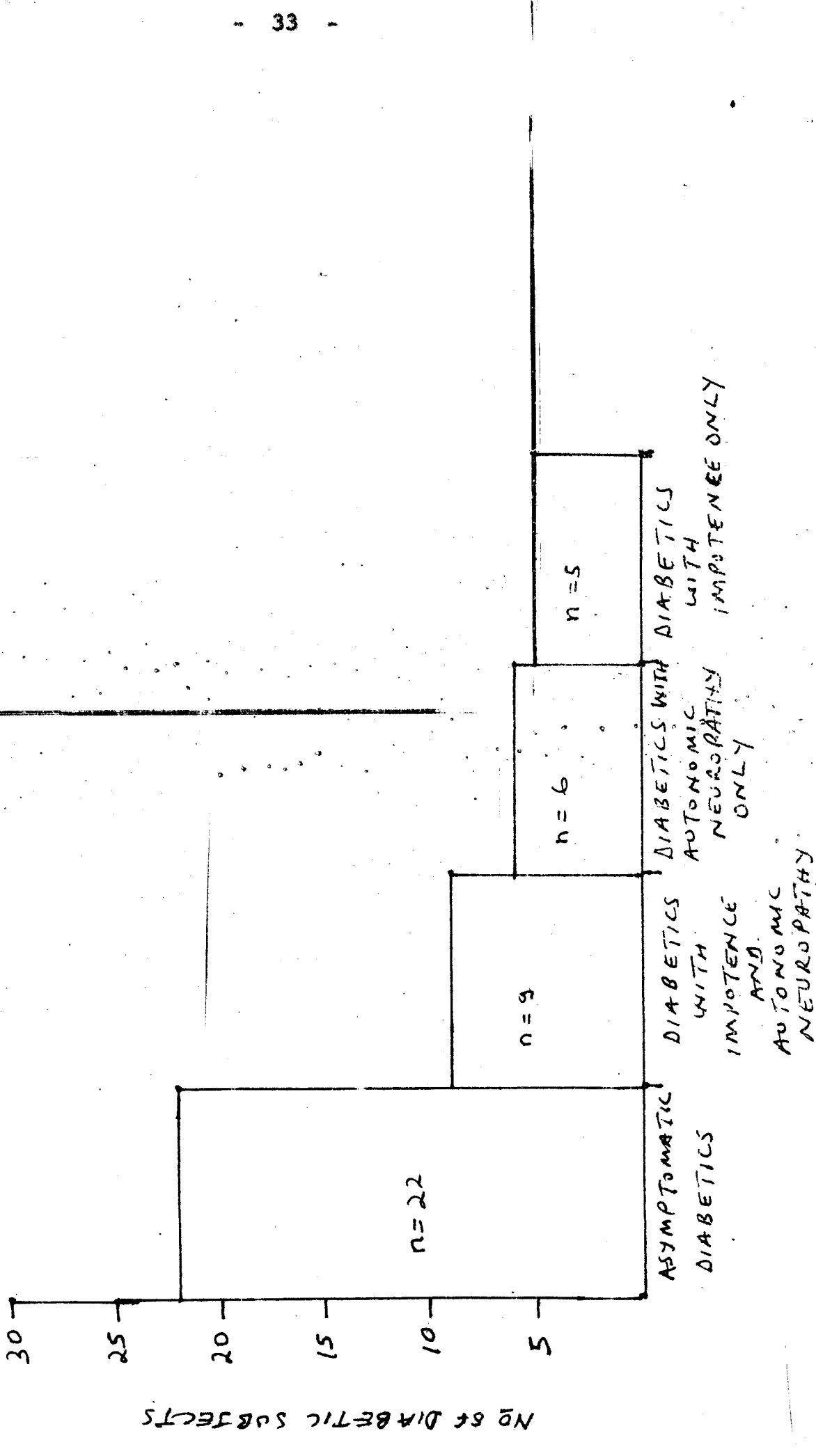


Figure iv.1 Histrogram of findings in study group

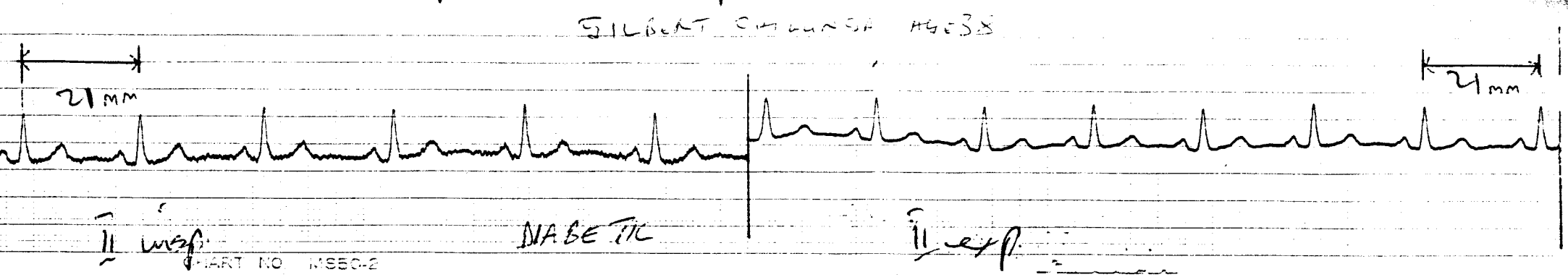
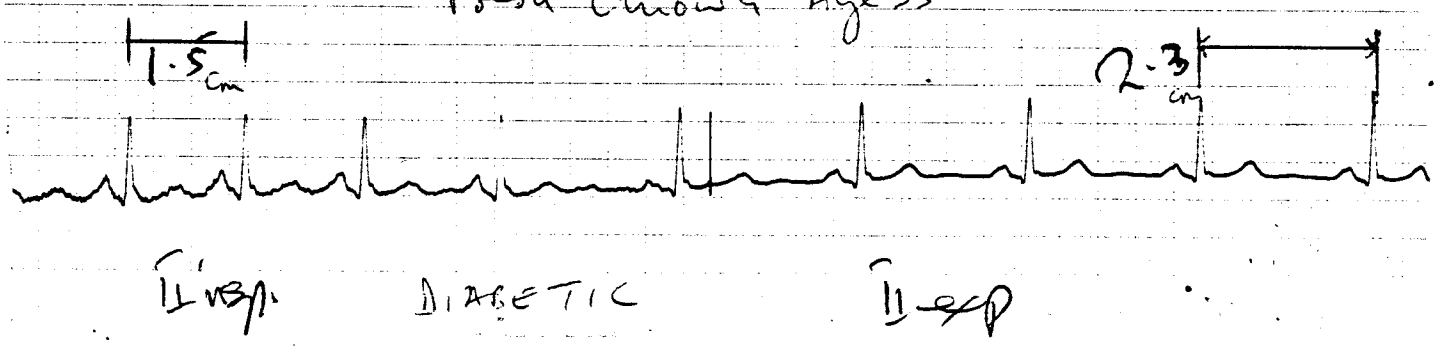


Figure IV·3 Electrogram of diabetic subject without autonomic neuropathy in deep breathing



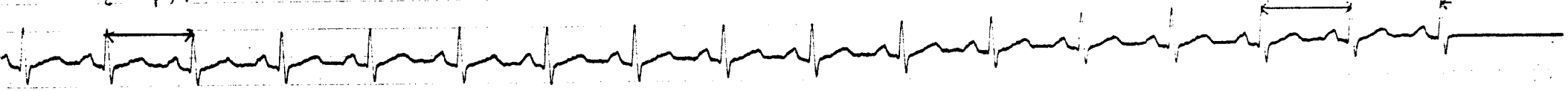
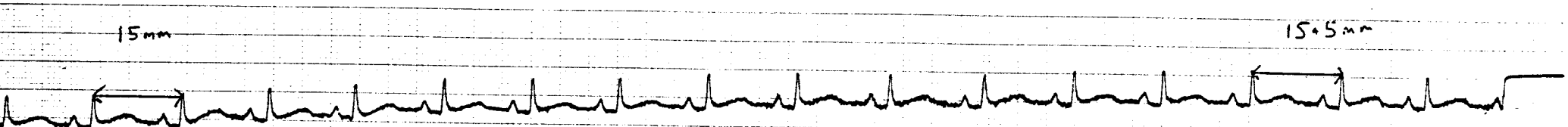


Figure IV.4 Electrogram of diabetic subject with normal 30:15 ratio



× Figure IV.5 Electrogram of ~~d~~diabetic subject with borderline 30:15 ratio

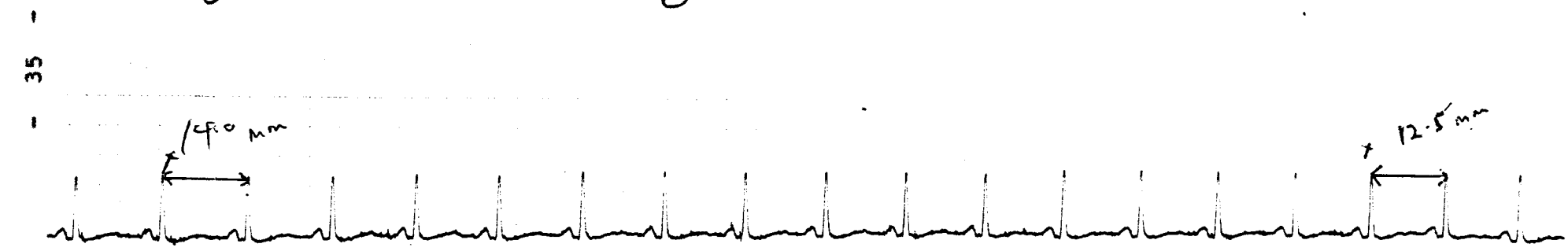


Figure IV.6 Electrogram of II Standing diabetic subject with abnormal 30:15 ratio

Table IV.2 Analysis of habits of diabetic subjects

	Diabetics with autonomic neuropathy N = 15	Diabetics without autonomic neuropathy N = 27
Diet (How strictly followed)	9 strictly 6 sometimes	~~2 very strictly~~ 12 strictly 13 sometimes
Intake of alcohol	5 yes 10 no	10 yes 17 no
Smoking	1 yes 14 no	3 yes 24 no

Table IV.3 Analysis of some habits in impotent subjects.

Impotent diabetics N = 14

Alcohol	Yes 5	No 9
Smoking	Yes 0	No 14

Table IV.4 Break down of results of tests for autonomic neuropathy.

Test	Abnormal	Borderline	Normal
E:I ratio N = 42	14	2	26
30:15 ratio N = 42	11	15	16
Systolic Bp N = 42	1	Nil	41

Table IV.5 Results of T-test for physical characteristics and autonomic neuropathy

	Controls N = 43		Subjects with autonomic neuropathy N = 15		Subjects without autonomic neuropathy N = 27	
	Mean ± SEM	Range	Mean ± SEM	Range	Mean ± SEM	Range
Age	34.6 ± 2.1	15 - 65	38.5 ± 2.7	22 - 57	38.6 ± 2.0	19 - 57
Duration			8.6 ± 0.9	5 - 15	8.8 ± 1	4 - 20
30:15 ratio	1.07 ± 0.008	1.03 - 1.3	1.007±0.02*	0.89 -1.22	1.07 ± 0.13	1.03 - 1.43
RHR	72 ± 2	45 - 120	77 ± 3	65 - 107	71 ± 2	50 - 107

*P = 0.0008 vs controls. (where not indicated, no statistical difference present)

CHAPTER V : SUMMARY

SUMMARY

The following is a summary of the results

1. Seven subjects among the diabetic subjects had evidence of peripheral neuropathy and six of these also had autonomic neuropathy.

2. Fifteen subjects from the same study group had autonomic neuropathy, (35.7%).

3. Fourteen subjects had impotence, (33.3%), from the study group while in the controls five subjects (11.%) complained of the same.

4. There was an overlap between the subjects with autonomic neuropathy and those with impotence; nine subjects had both impotence and autonomic neuropathy.

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CHAPTER VI : DISCUSSION

DISCUSSION

The study group of diabetics was taken from those attending the regular out patient diabetic clinic at the University Teaching Hospital, Lusaka, and were representantive of the male diabetic population. The study group and the controls were age-matched and comparable except for the diabetes of course. The various variables could therefore be compared and reasonable inferences made from the results.

It is generally true that the longer the duration of diabetes the more likely one is to develop neuropathy but in this study there was no significant difference between the mean duration of diabetes in those with and those subjects without autonomic neuropathy. Perhaps one of the reasons for this is that the subjects with autonomic neuropathy were few and another study is indicated were a comparison can be made between patients with short duration of diabetes, less than twenty years and those with diabetes of long duration, which may be put as more than twenty years.

With reference to the social habits inquired into that is diet, smoking and alcohol intake, the responses are given in the results. When broken down into the three main groups, the controls, the diabetic subjects with autonomic neuropathy and those without autonomic neuropathy, the figures were unfortunately not big enough for statistical analysis so there can be no firm conclusions drawn from them.

Nine of the fifteen subjects with autonomic neuropathy had symptoms of autonomic neuropathy. This group of diabetics with symptoms of autonomic neuropathy carries by far the worst prognosis of mortality among diabetic patients. A high prevalence of autonomic neuropathy and impotence has been found among diabetic subjects elsewhere.

The rates range from twenty to forty percent for autonomic neuropathy and upto forty percent for impotence (Chapter II).

In this study the prevalence of autonomic neuropathy was 35.7%, while that of impotence was 33.3%. Severe autonomic dysfunction, that is when both the sympathetic and parasympathetic systems are affected is rare. In this study only one subject had all three tests of autonomic function abnormal. He also had florid symptoms, like total impotence for the last ten years, gustatory sweating and evidence of peripheral neuropathy. Like in other studies, only few patients, (28%) volunteered the information about impotence. In the majority of patients this was only elicited on direct questioning.

Though diabetics can also be affected by other causes of impotence like psychological ones, autonomic neuropathy has been found to be the commonest cause accounting for up to 70% of cases. In this study 64.3% of the impotent diabetics had autonomic neuropathy suggesting that in this study group as well autonomic neuropathy is by far the

commonest cause of impotence. In the general population, 70% of cases of impotence is due to psychological reasons. In the control group, the prevalence was 11.6%, five patients, and of these only one subject had features of organic impotence, but not autonomic neuropathy though. Among the controls there was no one with autonomic neuropathy as ascertained by the 30:15 ratio and the blood pressure response to standing. The E:1 ratios could not be used to ascertain autonomic neuropathy among the controls because it was from the same figures that a normal graph was constructed.

In the diabetic study group seven subjects had evidence of peripheral neuropathy and six of these also had autonomic neuropathy. This means six of the total fifteen subjects of autonomic neuropathy had peripheral neuropathy, confirming in the diabetic subjects in Zambia what has been reported by other workers elsewhere (Sundkvist et al 1981).

A resting heart rate of more than 90 per minute may indicate autonomic neuropathy in a diabetic but in this study there was no significant difference in resting heart rate between the controls and the diabetic subjects. Although the mean resting heart rate in those with autonomic neuropathy was higher than in the controls and the diabetics without autonomic neuropathy (Table IV.1), this difference was not statistically significant. Perhaps a larger study would be more informative.

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The process of neuropathy is not reversible once it occurs and therefore prevention is of prime importance. Good control of glycaemia with drugs, exercise and diet is the main stay in the prevention of this and other complications of diabetes (S.E. Kahn et al 1983).

Glycosylated haemoglobin level is a good indication of diabetic control at least for the preceeding three months and although this has not been done in our patients, there are suggestions of poor control which might lead one to expect a higher prevalence of autonomic neuropathy than in more developed countries. Our diabetics frequently run out of medication, often wrong doses of insulin are administered and if the correct dose is given poor storage probably reduces it's efficacy and diet is often not strictly followed. However this study did not show any difference in the prevalences of autonomic neuropathy between the diabetics here and in the more developed countries, suggesting that there may be another factor here which gives some form of protection. However this can only remain conjecture at the moment pending further studies of this complication in our diabetic patients.

Although the disease process cannot be reversed some symptoms of autonomic neuropathy can sometimes be relieved. For example postural hypotension is best treated with fludrocortisone, gastric atomy responds well with metoclopromide and diarrhoea sometimes responds to the same drug.

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However western medicine can do little for impotence and when it occurs only counselling of the spouses may help. Penile prosthesis have been used in the United States with some success but this form of treatment is not widely available. It is perhaps not surprising that in our environment 80% of the patients had tried traditional medicine for impotence but with disappointing results; o only one patient said he noticed some improvement in performance.

In spite of our inability to treat autonomic neuropathy it's recognition is important, not only because it offers an explanation for the related symptoms but also to enable precautions to be taken to avoid it s more serious consequences. Hypoglycaemia is more dangerous in patients with autonomic neuropathy because of the absence of the early warning symptoms and classical signs. Further more cardio respiratory arrest in relation to anaesthesia and surgery has already been mentioned as a risk in patients with autonomic neuropathy. Precautions include patient education on some of the more amenable symptoms like as an example rising slowly from the supine position in those patients with postural hypotension and timed manual suprapubic compression in those with urinary retension. Physicians should also alert their colleagues in other specialities especially surgery when this risk is present. It is estimated that at least 50% of diabetics will have at least one operation in their life time (W.H.O. 1980) and awareness of the presence of autonomic neuropathy can prevent some fatalities.

CHAPTER VII : CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

This study has confirmed that autonomic neuropathy is a significant problem among Zambian diabetics and impotence is also a significant finding and occurs more frequently in patients with autonomic neuropathy.

It is suggested that all diabetics should be tested for autonomic neuropathy, particularly those with suggestive symptoms and whenever surgery is contemplated. Prospective studies are needed to measure the prognosis in patients with autonomic neuropathy in this environment and to determine the effect of improved control of diabetes on the progression of this complication.

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APPENDICES

CASE CARD FOR AUTONOMIC NEUROPATHY AND IMPOTENCE IN DIABETICS

Name:

Age:

Sex:

Marital Status:

STUDY NO:

HOSPITAL NO:

DATE:

Marital Status: Single/Married/Seperated/Widowed

Occupatibn:

Address: Postal Residential

Type of Diabetes IDDM/NIDDM DURATION

Treatment: - Diet only - Diet + O.H. - Diet + L.I. - Diet + S.
I-Other (Specify)

If O.H which one:

Insulin dose:

How strictly do you follow your diet?

- Not at all - Sometines - strictly - Very strictly

- Past Medical History

- Social History/personal - Alcohol intake Beer/Spirits Yes/No
- exercise non/mild/moderate/nigorous
- Smoking Yes/No

Family History:

Drug History

Complaints at Present

- Polyphagia
- Polyaresi
- Polydipsia
- Blurrying of Vision
- Numbness
- Pins and Needles
- Diarrhoea
- Gustatory Sweating
- Balanitis
- Weight loss
- Chronic cough
- Muscle weakness
- Recurrent furunculosis/carbuncle
- Impotence
- Ejaculatary dysfunotion
- Bladder dysfunction
- Other (Specify)

If impotence present

Duration

Before or after Diagnosis or as presenting complaint

Is it getting worse or better

If errectile partial or total or difficulty in maintaining erectio

Loss of morning erections

Affected by partner - Yes/No

Have you ever asked for help Yes/No

If yes what type of help

1. Traditional
2. Western
3. Other (Specify)

Loss of libido Yes/No

PHYSICAL EXAMINATION

Height: Weight BMI:

Resting Pulse

B.P. Lying:

Standing:

CVS RS GIT

CNS

Investigations:

DIAGNOSIS