

**Diabetes in the elderly.**

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**Diabetes in the elderly.**

**Dedicated to  
my parents.**



Diabetes in the elderly.

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## Diabetes in the elderly.

### Abbreviations used in this thesis.

<b>BDA:</b>	British Diabetic Association.
<b>BMI:</b>	body mass index.
<b>CI/CL:</b>	confidence interval/confidence limit.
<b>d:</b>	day
<b>DF:</b>	degrees of freedom.
<b>DM:</b>	diabetes mellitus.
<b>F:</b>	female.
<b>FBG/FPG:</b>	fasting blood/plasma glucose.
<b>GP:</b>	general practitioner.
<b>GTT:</b>	glucose tolerance test.
<b>h:</b>	hour
<b>HbA<sub>1c</sub>:</b>	glycosylated haemoglobin.
<b>IDDM:</b>	insulin dependent diabetes mellitus.
<b>IGT:</b>	impaired glucose tolerance.
<b>M:</b>	male.
<b>m:</b>	month.
<b>MOGTT:</b>	modified oral glucose tolerance test.
<b>n:</b>	number.
<b>NDDG:</b>	National Diabetes Data Group.
<b>NGT:</b>	Normal glucose tolerance
<b>NHANES:</b>	National Health and Nutrition Examination Survey.
<b>NIDDM:</b>	non-insulin dependent diabetes mellitus.
<b>OPCS:</b>	Office of Population Censuses and Surveys.
<b>P:</b>	Probability.
<b>RBG/RPG:</b>	random blood/plasma glucose.
<b>SD:</b>	standard deviation.
<b>WHO:</b>	World Health Organisation.
<b>y:</b>	year

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## Diabetes in the elderly.

### Chapter 1: the significance of diabetes mellitus in the elderly.

It is well recognised that there is a large elderly population in the United Kingdom; their numbers have grown dramatically during the present century. At the turn of the century, the retirement age was set at 65 years by Bismarck on the advice of Krups to avoid paying too many pensions, since the Prussian citizens would soon be dead [1]. However, now the population aged 65 years old and over comprises 15.8% of the UK population with 7.0% aged 75 or more [2]; these figures are expected to increase slightly over the next few decades (Figure 1.1) [3].

Figure 1.1: table of the size of the elderly population of England and Wales (numbers in millions).

Year	Age group (years)		
	65-74	75-84	85+
1951	3.2	1.4	0.2
1981	4.6	2.4	0.5
1991	4.5	2.8	0.8
2001	4.2	2.8	1.0
2011	4.5	2.6	1.1
2021	5.1	2.9	1.1

There have been several models of mortality and morbidity with advancing age. The view of Gruenberg [4] is that medical treatment saves lives but that illnesses strike those already disabled by chronic ill health which will occur anyway, so that extension of life is an extension of illness and disability. This "failure of success" view is in deep contrast to the model of Fries which is particularly optimistic and rosy [5]. Fries believes that previous premature deaths were generally due to infectious diseases which have since been greatly reduced by environmental, social and medical factors; now chronic illnesses are the major health problem, eg arteriosclerosis, emphysema, diabetes, and although inevitable, these conditions may be postponed by other environmental, social and medical factors. However, the age related decline in functional organ reserve continues giving rise to an exponentially increasing probability of death occurring as a stochastic event [6],

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originally described as the Gompertz function. Thus the model of Fries suggests that ill health will be postponed until the subject approaches the biological limit of their life, when the subject will experience a compressed period of morbidity prior to death.

Although these two views are quite opposite, they both suggest that chronic illnesses rather than mortality need to be the main target of healthcare activity [7].

Support for the model of Fries has been found in population studies in Melton Mowbray where improved morbidity and functional ability was found on two cross-sections of the elderly separated by only 7 years [8]. In a review of stroke epidemiology, it was shown that deaths from cerebrovascular disease have been declining for several decades in the UK and this was partly due to a declining incidence, as well as improved survival and changes in death certification practice [9].

Thus it appears that the aim of the British Geriatrics Society, adding life to years, [9a] is happening anyway, for whatever reason, and the previous picture of the elderly as "sans teeth, sans eyes, sans taste, sans every thing" [10] is now incorrect.

However, this picture may well be disturbed by diabetes. Several years ago diabetes in the elderly was a neglected area [11], but now non-insulin dependent diabetes and diabetes in the elderly are increasingly being recognised as a "wolf in sheep's clothing" [12,13]. Indeed, I have recently demonstrated that this analogy to a wolf is grossly unjust, since the wolf is neither common, nor a cause of morbidity or mortality to man, which is quite unlike diabetes mellitus [14].

Studies of known diabetic subjects in the British population show that 63% of known diabetic subjects are over 60 years old [15,16,17], and a survey of diabetic hospital in-patients being treated in Edinburgh found that 60% were aged 65 years or more [18]. Thus diabetes is a disease of the elderly.

Studies in other elderly European populations have shown that diabetes is common with a prevalence of approximately 18% in elderly white Americans [19-21] and from 7.6% to 30% in other European white populations [22-29]; however, the



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overall prevalence of diabetes in the elderly of the UK is not known. One problem is that approximately 50% of elderly diabetic subjects remain undiagnosed [20].

Poorly controlled diabetes and diabetic complications, both specific and non-specific, affect the quality of life. Elderly people with NIDDM may develop diabetic maculopathy which has been calculated to be 2.6 times as common as proliferative retinopathy as a cause of diabetes associated blind registrations [30] amongst the UK diabetic population of all ages. 12.5% of blind and partial sighted registrations in residents of Avon aged 60 or more were due to diabetic eye disease [31]. This is important, not only because preservation of vision is a key aim of the WHO health of the elderly expert committee [32], but also because it is treatable [33,34]. Correct treatment may prevent 73% of blind registrations due to diabetes [30].

Lower extremity amputations are quite correctly a major worry of elderly diabetic subjects; in Americans aged 65 or more, the amputation rate was 0.1% in non-diabetic people but 1.0% in people known to have diabetes [35], and the elderly had more extensive amputations than the young [35]. The effect of the amputation in the elderly is disastrous with only 5% becoming independently mobile [36], although rehabilitation was interrupted by death in at least 34%. In Scotland 80% of diabetic amputees were aged over 65; the relative risk of amputation was 27.4 comparing diabetic to non-diabetic subjects, and the 2 year survival after amputation was 57% [37]. However, careful foot care may prevent loss of limb by up to 50% [35,38,39].

The effect of these complications on British elderly known to be diabetic in Nottingham is that 16% are registered blind or partially sighted, 11% have or have had foot ulcers, 35% have absent vibration sense at the ankles and 19% have proteinuria [40].

Similarly, in the elderly known to be diabetic in Oxford 32% have a visual acuity worse than 6/12, 4% have lower extremity amputations, 7% have foot ulcers and 80% have some form of diabetic specific or non-specific complication [41].

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Thus diabetes affects the quality of life of elderly sufferers, and also affects how they spend their life; the elderly diabetic is likely to spend 2 to 3 times as long in hospital as his non-diabetic peers [42].

Diabetes may also shorten the life of the elderly subject [43] but the full effect of this is uncertain due to underascertainment of diabetic subjects; the general population undoubtedly contains many subjects with unrecognised diabetes and impaired glucose tolerance who have increased mortality [44] thus blurring any differences between diabetic subjects and the general population.

It has been found that deaths from diabetic ketoacidosis occur predominantly in the elderly [45] in whom their diabetes had not been recognised and studies show higher blood glucose levels on admission of elderly diabetic subjects in diabetic ketoacidosis suggesting delay in identifying the problem [45,46].

Despite the above, several authors label NIDDM in the elderly as mild [47,48].

Thus diabetes in the elderly is an important area; it affects many citizens, it is a cause of morbidity which may be avoided, and a cause of death, some of which could be avoided. Its full significance may be underestimated by many. It is interesting to note that the St Vincent declaration of the WHO [49] with its "Health for All" manifesto quite rightly emphasizes the needs of diabetic children, but does not mention the needs of the elderly diabetic person who has appreciable comorbidity in terms of physical, cognitive and social problems [40].

The overall prevalence of diabetes in the elderly of the UK is unknown and therefore I wish to define the size of the problem by examining an average UK population; this has to be by glucose tolerance testing, since this is how diabetes is defined [50,51]. It would also be important to examine whether non-recruitment was likely to bias this prevalence, since full participation in any screening survey is unlikely. Glucose tolerance testing would be impractical in everyday use to screen a population, and so what is the role of other screening methods, such as urinalysis, and glycated products? It may be that no screening test is particularly good; therefore, are there any features of undiagnosed diabetic subjects that would help one target high risk patients for glucose tolerance testing? A screened

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#### Diabetes in the elderly.

population would also allow more thorough examination of the effect of abnormal glucose tolerance on morbidity and mortality.

However, there is little point in finding diabetic subjects if their care is inadequate; how good is the care offered by geriatricians, general practitioners and diabetologists to elderly diabetic subjects?

The following thesis aims to answer the above questions on the significance of undiagnosed diabetes mellitus on the healthcare of the elderly.

The prevalence of diabetes.

## Chapter 2: the prevalence of diabetes in the elderly.

### 2.1: previous studies on the prevalence of known diabetes in the elderly.

With the large number of elderly people in the United Kingdom, it is important to ascertain the total prevalence of diabetes mellitus in them, not only from an academic point of view, but also so that consequent health care can be planned.

The reported prevalence of diagnosed diabetes in the elderly varies from around 3% in Southall, Poole and Oxford to 9% in Leicester [15-17,52,53].

A general practice based study in Poole [16] identified diabetic subjects by repeat prescriptions for hypoglycaemic agents and testing equipment, by general practitioner (GP) diabetic registers and by hospital diabetic clinic lists (Figure 2.1).

Figure 2.1: table of results of Poole diabetes survey (numbers of subjects).

Age	Population:		Diabetic subjects:		Prevalence(%)	
	Male	Female	Male	Female	Male	Female
65 - 74	4035	5169	134	128	3.32	2.48
75+	2234	3973	102	115	4.57	2.89

However, diabetic subjects on diet alone, who may not bother to monitor their glycaemic control (particularly if they are elderly) may be underrepresented in this survey. It was checked that diabetic patients fulfilled the WHO criteria for diabetes mellitus. The size of the population sample was obtained from the number of people registered with each practice; this probably overestimates the size of the population. Family practitioner committee lists, or general practice patient registers may be inaccurate since patients often do not inform the authorities if they move, emigrate, or die [54,55]. These errors are particularly likely to occur in the elderly; for instance, in City and Hackney in 1986 there were 1337 residents aged 85 or more, but the family practitioner committee list contained 3018 people [54]. It is interesting to note that in the 75+ age group, the male prevalence is much higher than female (4.57% versus 2.90%; 2 tailed Fisher's exact  $P=0.0007$ ) despite studies showing similar prevalences in each sex

### Diabetes in the elderly.

[20]; this could relate to a higher ascertainment rate in men, or the female population at risk could be inflated by more dead elderly females since the problem of enforcing death notification is well recognised [54].

This study was also reported alongside the Oxford survey [17], and on this occasion the results are expressed for different age groups (Figure 2.2).

Figure 2.2: table of results of several UK diabetes surveys (numbers of subjects).

Age	Oxford:		Poole:		Southall:	
	Pop	DM	Pop	DM	Pop	DM
60-69	4080	90	9970	200	3205	76
70-79	3107	131	7645	270	2510	93
80+	1331	38	3002	96	865	51

Note: Pop = number of subjects in population.  
DM = number of diabetic subjects.

The Oxford survey used a postal questionnaire in one geographical area in 1982 asking the residents if they were diabetic. Further diabetic subjects were sought using general practice diabetic registers, insulin prescriptions and hospital activity analysis records; it is noteworthy that in 10 to 23% of diabetic hospital admissions, the diagnosis of diabetes did not occur in the hospital activity analysis data [56]. There is no evidence given that these subjects were checked that they were diabetic; although they probably were diabetic, one lonely retired non-diabetic gentleman volunteered that he was diabetic because he fancied the medical check up that the diabetic subjects received [HAW Neil, personal communication].

The survey population was defined by the Office of Population Censuses and Surveys (OPCS) 1981 census. The Oxford population was circa 98% Euroid. Although the authors state that under-ascertainment of known diabetes is to some degree inevitable with a rate of 5 to 10%, they do not detail how they found the known diabetic subjects not revealed by the study methods; a previous survey in Oxfordshire using many methods of ascertainment of known diabetes [52] found that the questionnaire missed 8% of the known diabetic subjects. The Southall

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survey [15] estimated underascertainment at about 16%. They do note that recent prevalences in Oxford, Poole and Southall are higher than in Edinburgh in 1968 [57] and in Birmingham in 1962 [58]; this could be due to an aging population, improved survey methods, longer survival of diabetic subjects, improved detection of diabetic subjects, or a genuine increase in the overall prevalence of diabetes. The increase in prevalence of known diabetes is probably greater than the authors implied since the criteria for diabetes were modified in 1979; thus many people previously labelled diabetic would now be classified as having impaired glucose tolerance (IGT) [59].

The Southall survey [15] was based on a house to house enquiry in 1984 to ascertain whether the prevalence of known diabetes differed between Asians and Europeans. Investigators knocked on doors and asked if any diabetic subjects were resident; if so further patient details were obtained.

This method of identifying subjects with diabetes was scrutinized in a second ascertainment survey by checking 815 known diabetic patients who had attended a diabetic clinic: at least 16% of these patients had been missed on the first enquiry. 20 diabetic subjects denied being diabetic on both first and second enquiries, and it has previously been noted that if diabetic patients are discharged from clinic, they may consider that they have been cured [60]. 93 diabetic people had not been identified as diabetic on the first enquiry; it is probable that another member of the household had answered the door initially, since the NHANES II survey had found that the rate of self reported diabetes was much higher than the rate reported by the interviewee for other household members [20]. Finally, if an investigator knocks on ones door asking for diabetic subjects, one is likely to deny being diabetic to save the bother.

The population sample was defined by the 1981 OPCS census, and the ethnic composition of the population estimated from the place of birth of the head of the household, eg if the place of birth was East Africa, the person was Asian which is quite likely but not definite. It is a pity that the investigators did not survey the age and origin of all the residents, but that would have entailed much more work,

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which was being done by volunteers. The prevalences are given both crude, and adjusted for the 3½ years between the 1981 census and 1984 survey. Many studies use OPCS census data as the denominator of their prevalence data, and correct for the interval between census and diabetic survey by assuming the whole population ages the same interval [15,53]; this method does not appreciate (although the Southall authors did [15]) that some of the population die or move, and could thus overestimate the size of the study population and falsely minimise the prevalence in the elderly, in particular. Thus the adjusted prevalence probably underestimates the age specific prevalence, and the crude prevalence probably overestimates this.

Despite these problems, all of these studies fulfilled their aims and also took much effort; for instance, the Southall survey [15] involved calling on 18,538 households, the Oxford survey questioned 40,079 subjects by post [17], and the Poole survey [16] involved the investigator examining all 917 diabetic subjects. These 3 studies give similar prevalences to a small GP study in Maidenhead based on the practice list and diabetic register finding 108 diabetic subjects in a population of 2844 aged 60 and over [61]; of course interested general practices find more diabetic subjects among their patients than disinterested practices [62]. The Leicester survey [53] was based on a geographical area in north-east Leicester; the population base was derived from 1981 OPCS census data, and diabetic subjects were identified from the records of the diabetic health visitors who have been active here since the early 1950's [63]. In 6324 white Caucasians aged 65 or over, there were 666 diabetic subjects giving crude and adjusted prevalences of 10.5 and 9.0% respectively.

The prevalence of diagnosed diabetes in the elderly is significantly higher in Leicester than in Southall, Poole and Oxford. This difference could be due to a genuinely higher incidence of diabetes from a geographical cause or due to a higher rate of diagnosis in Leicester. These surveys used differing methodologies and it may be the use of the diabetic health visitor records in Leicester to identify people with known diabetes which explains the difference. These specialist

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community care health visitors have been informed of all newly found diabetic patients by hospital staff and general practitioners for the last 38 years [63] and maintain their own accurate records; it has previously been noted that nursing staff are better at completing records than medical staff [52]. Thus there is a high local awareness of diabetes, and the patients continue to be followed up, not being allowed to forget their diabetes.

The difficulties of ascertaining the numbers of known diabetic subjects were summarised in a study of 4 general practices using questionnaires, practice records, prescriptions for diabetic items and hospital diabetic registers [52]. Overall, 105 diabetic subjects were found, but 8 of these were missed on the questionnaire survey (4 did not reply, 4 denied diabetes), and only 76 would have been identified by the usual survey methods of GP diabetic registers and repeat prescription monitoring.

## **2.2: previous studies on the overall prevalence of diabetes in the elderly.**

I have discussed the prevalence of diagnosed diabetes, but non-insulin dependent diabetes mellitus (NIDDM), the predominant form of diabetes in the elderly, may be asymptomatic and underreported. It has been appreciated since 1921 that screening for diabetes in the elderly is worthwhile [64]; unfortunately, many of the prevalence studies on diabetes in the UK have only reported on known diabetic subjects. Many screening surveys were performed in the 1960s but these are now believed to be flawed due to subject preselection by positive urinalysis only and by the use of diagnostic criteria prior to the introduction of IGT [58,65-73]. However, in the past blood glucose measurement was difficult and initially required up to 500 ml of blood, making blood glucose based screening surveys impractical [74]. Some previous surveys have also been incomplete in that they identified many unknown diabetic subjects, but did not give the numbers of known diabetic subjects, the size of the population or the age structure of the population. Some studies have been representative of large populations, but some have applied to very small special populations. Nonetheless, all of these surveys



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are likely to have involved considerable work, and can still yield useful information. The Bedford diabetic survey [66] identified many subjects with impaired glucose tolerance whose survival and progression to diabetes could be followed. The 2nd Birmingham survey examined subjects with no glycosuria [70], and their findings can be reinterpreted with an 11.1 mmol/l cut off; no one under 50 was found to be diabetic, but of 155 subjects aged 50 to 69, 1 was diabetic (old criteria gave 30), and of 46 subjects aged 70 and over, 5 were diabetic (old criteria gave 18); thus diabetic subjects missed by urinalysis tend to be elderly, and the later criteria produce far fewer diabetic labels than earlier criteria. Finally, the Ibstock survey [73] examined a mining village in Leicestershire and found 11 known diabetic subjects in 408 residents aged 65 or more giving a prevalence of 2.7% (95% CI 1.35 to 4.77%).

The total prevalence of diabetes has been ascertained in some western countries by population screening with glucose tolerance tests (GTT). Some investigators have used the fasting blood glucose to estimate the prevalence of diabetes but this misses the age related increase in prevalence of diabetes [20,21] and is discussed further in Chapter 4. Figure 2.3 shows the prevalence of diabetes in various elderly populations using the latest WHO/NDG criteria [50,51] and one can see that the prevalence of diabetes varies from 7.6% in 67 year old Swedes, 17.9% in white Americans aged 65 to 74 years, to 30% in elderly Finns [20-28]. These prevalences in various "Euroid" populations differ widely, and can not be used to estimate the prevalence in the UK.

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Figure 2.3: table of the prevalence of diabetes in different Europid populations.

Study	Year	Ref	Age	Sex	Recruit rate (%)	Diabetes rate (%)	IGT rate (%)
NHANES II USA	1976-1980	20	65-74	M+F	56	17.9	23.0
California USA	1972-1974	21	60-89	M+F	83	16.1	-
Fredericia Denmark	1981-1982	22	60-74	M+F	93	7.2	- F
Glostrup Denmark	1967-1977	23	70-80	M+F	64-73	10.0-12.0	25-36 U
Tampere Finland	1977	24	85+	M+F	83	17.0	- F
Kuopio Finland	1986-1988	25	65-74	M+F	71	17.8	20.8
East/West Finland	1984	26	65-84	M	94	29.8	31.8
Gothenburg Sweden	1980	27	67	M	79	10.8	14.2
Amsterdam Holland	1985	28	65+	M+F	?	23.6	- D

Note: F=FBG based survey.

D=recruitment details scanty.

U=previously undiagnosed diabetic subjects only recorded.

There have been two recent screening surveys in the UK, but neither concentrated on the elderly.

The first study was done in Islington in 1985 [75] to assess the prevalence of diabetes mellitus in a North London general practice. A sample was drawn from the age/sex register of people over the age of 40, stratified by age and sex; known diabetic subjects were identified (although whether or not these subjects fulfilled WHO criteria is not stated), and the remainder were offered a modified oral glucose tolerance test (MOGTT). The sample selected consisted of 1908 subjects but of these 50 were dead, 41 were known diabetic subjects (including 3 dead patients), 176 had recently been removed from the register, 25 were too ill, 183 refused testing, 37 failed to attend, 117 had left the area without re-registering, and 198 could not be traced anywhere; these figures exemplify the problems of general practice population registers, as previously discussed, and the problems of

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patient recruitment. 1084 were tested of whom 74.4% were of North European origin, and the remainder were predominantly Afro-Caribbean. Of 451 subjects aged 60 or more, 18 new diabetic subjects were found, giving a prevalence of previously undiagnosed diabetes of 4.0%; the number of previously diagnosed diabetic subjects is not stated for this age group but the authors say that 48% of the diabetic subjects aged 40 or more were known. The prevalence of diabetes mellitus was higher in Afro-Caribbeans than in Caucasians, a common finding [20], although unfortunately the authors of the Islington survey did not give a specific breakdown of the results by race [75].

The second study was done in Coventry in 1988 [76] to look at the difference in prevalence of diabetes in Asian and European residents. Investigators knocked on all the doors (up to 10 times, if necessary) in one electoral ward and collected basic personal details and a random capillary whole blood glucose level. If the random glucose was 6.0 mmol/l or greater within 2 hours of eating or 4.4 mmol/l or greater more than 2 hours after eating, then a GTT was performed. 66% of the elderly European population consented to screening.

As a check on this prescreening procedure, 222 subjects with acceptable random blood glucose levels were offered a GTT; 130 subjects (59%) accepted and 2 subjects (both aged over 70) were found to be diabetic [77]. The age, sex, and race of these test subjects was not given in the original reports [76,77], but later the authors examined their results specifically for the elderly [77a], and calculated that adjusting for the "negative screeners" subjects who had raised GTT results at two hours, would increase the prevalence of diabetes in the elderly of Coventry by 3%. Since the fasting blood glucose increases less with age than the 2 hour glucose [20], one would expect that the diabetic subjects missed by the prescreening "pseudo-fasting" blood glucose level would be the elderly.

The subject's assertion that they were diabetic was confirmed by a random blood glucose greater than 8.0 mmol/l, by the taking of hypoglycaemic medication or by general practitioner confirmation. The reason for the 8 mmol/l cut-off is not stated. In a study on gestational diabetes, of 3 pregnant subjects with mid-

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afternoon random plasma glucose levels greater than 8.0 mmol/l, only 2 were diabetic, but a further 9 diabetic subjects had glucose levels 8.0 mmol/l or lower [78]; thus the random plasma glucose will miss diabetic subjects at this cut-off, although those with higher levels are likely to be diabetic. The taking of hypoglycaemic medication does not necessarily prove that the subject is diabetic; I have personally met a lady in her 70s with normal glucose tolerance on formal testing who was taking glibenclamide for her renal glycosuria, and there are a case reports of patients taking insulin or sulphonylureas with normal glucose tolerance [79,80] including one man who took insulin for 50 years unnecessarily [81]. If the patient has the false belief that they are diabetic, it is highly likely that they obtained the misinformation from a medical practitioner; thus medical practitioner confirmation is probably worthless. Of 100 self reported type 2 diabetic Americans, 19 actually had normal glucose tolerance on formal testing [20]. Thus if a subject states that they are diabetic, one really has to study the original records and results to see upon what basis the diagnosis has been made.

One other feature of the Coventry study relates to the population used which had a very high migration rate of 20% and very low socioeconomic status; the area was amongst the most socially deprived 12 of the 9,000 English electoral wards [D. Simmons, personal communication]. Despite this, the study fulfils its aim, which was to compare the racial variation in diabetes mellitus, and gives valuable data on the prevalence in the elderly in one geographical area; again it involved a great deal of work in that 3993 individuals were approached and 3372 were screened. There were 609 Europids aged 60 to 79 years and 27 were known to be diabetic; 384 were screened and 11 new diabetic subjects were found giving a total prevalence of diabetes of 7.0%. This result is similar to that of the Islington survey where 4% were found to have previously undiagnosed diabetes, and a similar number were already known to have diabetes [75].

I therefore decided to determine the prevalence of diabetes in a sample of elderly people more representative of the UK population in terms of sociodemographic variables. To investigate the prevalence of diabetes mellitus, it is necessary to

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state the nature of diabetes, how it is defined, and how this definition is applied in practice.

#### **2.3: definition of diabetes mellitus in the elderly.**

It is well known that diabetes is a tendency to hyperglycaemia, but the distinction between normal and diabetic has previously been a grey area. For a long time the cut off value for the two hour blood glucose was somewhere around 130 mg% [82], although in the mid 1970s, diabetic experts were using up to 17 different methods to perform and interpret a glucose tolerance test (GTT) [83]. The situation was vastly improved in 1979 when the National Diabetes Data Group (NDDG) in the USA introduced their criteria [50] and the World Health Organisation (WHO) introduced their criteria the following year [84]. The first important advance was that everyone was now likely to be using the same criteria; even if they were not correct, everyone was talking about the same thing from then on [84]. The second major advance was the formal definition of the concept of impaired glucose tolerance for two hour venous plasma levels of 140 to 200 mg% [50,84]. 16% of subjects previously thought to have diabetes in a population under surveillance for diabetes were now reclassified as having IGT [59]. The two hour figure of 200 mg% translates to 11.1 mmol/l; initially the 1979 WHO figures were rounded off to the nearest whole mmol/l [84], but in 1985, the genuine conversion was used [51].

Diabetes is more than a tendency to have an elevated plasma glucose, it is also a tendency to develop specific and non-specific complications. Several population based studies performed GTTs and examined the subjects later for diabetic retinopathy. Dorf *et al* found that the prevalence of retinopathy increased dramatically with GTT results greater than 11.1 mmol/l in Pima Indians [85]. However some subjects with lower blood glucose results had retinopathy, and there were some flaws in the study; the interval between GTT and fundoscopy is not stated and thus subjects with impaired glucose tolerance might have converted to diabetes in the interim since the rate of conversion is approximately 6% per

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year in Pima Indians [86]; the blood specimens were left up to 12 hours before centrifugation, which may reduce the measured glucose level and misclassify diabetic subjects as non-diabetic. An improved study on Pima Indians reported on funduscopy changes 3 years after the GTTs were performed, without leaving the blood specimens to stand [87]; again this found that the 11.1 mmol/l cut-off distinguished from those who would or would not develop retinopathy, but also very importantly demonstrated that the fasting blood glucose was meaningless (Figure 2.4) regarding future development of retinopathy. The role of the FPG is discussed further in Section 4.3.

Figure 2.4: contingency table of results of glucose tolerance tests in Pima Indians (numbers of subjects) and later retinopathy.

		2 h plasma glucose (mmol/l)	
		<11.1	11.1+
fasting plasma glucose (mmol/l)	<7.8	159 (0)	22 (2)
	7.8+	1 (0)	38 (5)

Note: numbers in parentheses are number with retinopathy 3 years after GTT.

These studies are highly important, but they do not look at European populations. Follow up of both the Bedford and Whitehall studies revealed that those with GTT results above 11.1 mmol/l developed specific diabetic complications (retinopathy), but subjects with GTT results between 7.8 and 11 mmol/l did not [88,89]. Thus the importance of 11.1 mmol/l is that it separates those with a predisposition to diabetic specific complications from those without this tendency, although there is still an excess of non-specific diabetic complications in the impaired group [44,90]. It should be noted that the cut-off value of 11.1 mmol/l was reached by examining longitudinal studies, but the cut-off between normality and IGT was reached by consensus of experts [84] (Figure 2.5).

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Figure 2.5: table of diagnostic values for 2 hour post 75 g glucose load blood sample (mmol/l).

	Whole Blood:		Plasma:	
	Venous	Capillary	Venous	Capillary
Diabetes	10.0+	11.1+	11.1+	12.2+
IGT	6.7-10.0	7.8-11.1	7.8-11.1	8.9-12.2

So diabetes is defined by a venous plasma glucose of 11.1 mmol/l or more 2 hours after ingestion of a 75 gram glucose load. Ever since Spence [64] first noted that the elderly had elevated blood glucose levels, there has been debate regarding the blood glucose values required to make the diagnosis in the elderly [91]; several have argued that since the average values are higher in the elderly, the diagnostic levels of blood glucose should be higher [59,92,93]. This argument may be incorrect since most illnesses are commoner in the elderly and one does not generally alter the diagnostic criteria. If one examines populations with a very high incidence of NIDDM, such as the Pima Indians or Nauru Islanders, who have not previously been diagnosed as diabetic, then the results of mass glucose tolerance testing reveal a bimodal distribution at all ages including the elderly which is not seen in other populations due to their small numbers of undiagnosed diabetic subjects [85,94,95]. The cut-off value of 11.1 mmol/L does actually separate normoglycaemic and diabetic populations (each with a Gaussian distribution of 2 h values) in different age groups, suggesting that the WHO criteria apply in the elderly as well as the young. Although the longitudinal studies of GTT result and development of retinopathy [85,87,88] examined subjects of all ages, the number of elderly subjects was small and their development of retinopathy was not independently assessed. Since population studies of blood glucose levels support similar diagnostic criteria in young and old, and since these same criteria applied across all ages define subjects likely to develop specific diabetic complications, I personally believe that they apply to the elderly. However, it would be interesting to follow up a cohort of elderly with known GTT results to confirm this belief.

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**2.4: practical application of the glucose tolerance test.**

The WHO criteria do not give exact guidelines on performing a GTT, just how to interpret it. Factors such as timing, type of load, glucose assay, specimen storage, antecedent diet, and working definition of IGT have to be considered, and the practical application in a diabetes screening survey has to be assessed.

**2.5: time of day for performing GTT.**

As with many biological functions, there is a diurnal variation in response to a glucose load with the glucose levels attained being higher in the afternoon related to a delay in insulin release [96,97]. Thus GTTs should be performed in the morning; indeed this is usually the case except for one notable study showing a very high prevalence of diabetes in Finland [26]. This is also helpful regarding patient compliance; if the glucose is taken after an overnight fast, then it is only a modified breakfast, but later on in the day, the subject would have to deliberately fast, which they might not be trusted to do.

**2.6: diet preceeding GTT.**

It is recommended that subjects prior to a GTT take a diet containing 300 g of carbohydrate per day for 3 days; I have never seen a screening study attempt to comply with this. Fortunately it has been found that preceeding diets with as little as 50 g carbohydrate per day have a negligible effect on glucose tolerance [98].

**2.7: type of glucose load for GTT.**

The 1985 WHO criteria do not now specify the type of glucose or how it should be administered [51], although in 1965 they recommended glucose monohydrate for the 50 g load [82]. The difference between anhydrous glucose and glucose monohydrate may cause a difference of 10% in the amount of glucose administered [99]. Although it is known that the coefficient of variation of the blood glucose level post load is much better with a 100 g load than with 75 g or 50 g loads [100], the result of using hydrous or anhydrous forms of glucose is not



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known. However, I would use the higher load, ie 75 g of anhydrous glucose, since it is likely to give less variation. A disadvantage of using 75 g of medicinal glucose is that it is nauseating; of 10 subjects given this, two vomited the load [G. Fancourt, personal communication, 1989]. However, in 1921 it was noted that cane sugar, starch, and potatoes gave similar results to glucose when used as the carbohydrate load for a GTT [101]; at this stage a potato tolerance test was suggested, but did not become widely accepted. In 1927 a Newcastle pharmacist invented Lucozade as a non-nauseating glucose source for the sick patient [102]; this is a solution of partially hydrolysed starch which is rapidly digested to glucose. Lucozade also contains flavourings and preservatives including caffeine and sunset yellow colouring, which might interfere with a GTT, but the results using Lucozade were not significantly different from results using a solution of glucose monohydrate [103].

The final advantage of Lucozade is in terms of simplicity and patient acceptability; Lucozade is well known to most British people and its use in a GTT does not involve trying to dissolve a carton of medicinal glucose in warm water.

Thus 388 mls of Lucozade was used as a 75 g anhydrous glucose load rather than 353 mls which is a 75 g glucose monohydrate load.

### 2.8: storage and type of blood samples from GTT.

It is generally accepted that the plasma glucose level will remain constant if kept in a fluoride oxalate tube at room temperature for several hours, and even overnight [104,105]. This has recently been questioned and it was found that the whole blood glucose level remained stable at 3 hours but not at 6 hours at room temperature [106]; the decrease in glucose was most marked for low concentrations and was only 5% for glucose levels between 12 to 18.4 mmol/l. But what is the effect of storage in different ambient temperatures on plasma glucose levels?

Venous blood samples were taken from treated diabetic subjects, and divided into seven fluoride oxalate tubes. The plasma was separated immediately, and also

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after storage at room temperature and in a car after both 4 and 7 hours; after separation the plasma was frozen immediately, and later the glucose level was measured on a Beckman analyser (glucose oxidase method). It was found that the glucose level remained fairly stable for up to 7 hours at room temperature (average coefficient of variation 2.6%), but if the sample was left in the sun, the glucose level dropped slightly more (average coefficient of variation 3.4%) (Figure 2.6).

Measuring the glucose level ten times on a standard 10 mmol/l glucose solution gave an average coefficient of variation of 0.7%.

Haemolysing the specimen by passing the blood 10 times through a 19 gauge needle until at the hue of a rosé wine was obtained, revealed an average coefficient of variation of 3.7% from the non-haemolysed specimens.

Figure 2.6: effect of storage on blood glucose measurement.

Subject	Initial glucose (mmol/l)	Room samples glucose (mmol/l)		Car samples glucose (mmol/l)	
		4 h	7 h	4 h	7 h
MMI	17.3	17.2	17.1	16.8	16.5
PFE	13.4	13.5	13.2	13.3	14.0
AFU	9.1	8.9	9.0	8.9	9.0
JAC	9.6	9.8	9.5	9.5	9.4
IHI	13.4	13.0	13.8	13.7	14.0
JKI	4.2	4.0	4.1	3.7	4.2
JJO	11.4	11.2	11.0	11.1	10.7
LCR	16.8	16.1	16.5	16.4	16.0
FNA	6.3	6.0	6.6	6.3	6.4
NKA	12.1	11.6	12.1	11.7	11.7
RTU	11.1	10.9	10.6	10.7	10.5
MM2	11.3	11.2	11.1	10.8	11.4
Coefficient of variation (%)		2.6	2.2	3.4	3.1

The actual type of specimen also affects the result. Plasma glucose levels are commonly used with the significant level for a MOGTT being 11.1 mmol/l. It is possible to measure venous whole blood glucose, capillary plasma glucose and capillary whole blood glucose with significant levels at 10.0, 12.2, 11.1 mmol/l respectively [51] (Figure 2.5).

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However, when using these conversion values, it was found that capillary samples gave a lower incidence of abnormal glucose tolerance and venous whole blood gave a higher incidence compared to venous plasma [107]. Plasma samples are preferable to whole blood samples since any change in the blood glucose concentration is not blunted by the dead space of the red cells, and the whole blood glucose level increases as the haematocrit decreases [104]. The NDDG criteria recommend the use of plasma glucose [50], and one textbook [104] recommends the use of plasma glucose in a venous sample. The disadvantage of using plasma levels is the separation of the plasma, but this takes only a short time.

### 2.9: measurement of glucose level for GTT.

The WHO criteria do not specify the method to measure the glucose concentration. Before 1950 the Folin Wu method was commonly used; this used the chemical reduction of copper by glucose; however, any other reducing agent present elevated the result. Next the Somogyi-Nelson method used a similar copper reduction, but other reducing substances were first removed by precipitation with barium hydroxide and zinc sulphate; this was more or less a true glucose result. Recent autoanalysers such as the Technicon use the Hoffman method which is a ferricyanide reduction to ferrocyanide by glucose and gives similar results to the Somogyi-Nelson method. The most specific method is however the glucose oxidase method which is an enzymatic process totally specific for glucose; the previous chemical methods can still give falsely high readings in the presence of reducing agents such as fructose, galactose, glutathione and creatinine [104]. A set of reference ranges for the different methods is given in Figure 2.7.

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Figure 2.7: table comparing fasting blood glucose levels from different methods of glucose measurement.

Method :	FBG (mg%)	FBG (mmol/l)
Folin Wu	80 - 120	4.44 - 6.66
Somogyi-Nelson method	60 - 100	3.33 - 5.55
Hoffman	65 - 105	3.61 - 5.83
Glucose oxidase	60 - 95	3.33 - 5.27

Note: 1 mg%=0.0555 mmol/l glucose; FBG=fasting blood glucose.

There were four options for obtaining the plasma glucose levels in the Melton population survey; these were BM stix, a blotting paper technique, capillary tubes and formal venepuncture..

#### 2.10: use of BM stix for glucose measurement

The use of BM stix (Boehringer Mannheim, Lewes, Sussex, UK) was examined; these do not entail formal venepuncture, but one does have to wait two minutes for the colour reaction to occur. According to the manufacturers, the BM stix give glucose results similar to plasma rather than whole blood. In my hands the average coefficient of variation compared to formal laboratory plasma glucose measured using a glucose oxidase method was 16.2% (Figure 2.8) with no bias towards either high or low variation.

Figure 2.8: table comparing results obtained from BM stix and formal glucose level.

Subject	Formal glucose (mmol/l)	BM stix result (mmol/l)	Variation (%)
MM1	17.3	15	-13.3
PFE	13.4	13	-3.0
AFU	9.1	10	9.9
JAC	9.6	13	35.4
IHI	13.4	13	-3.0
JKI	4.2	3	-28.6
JJO	11.4	11	-3.5
LCR	16.8	17	1.2
FNA	6.3	8	27.0
NKA	12.1	17	40.5
RTU	11.1	13	-17.1
MM2	11.3	10	-11.5

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The use of meters to read the BM stix was considered since others have found them useful [26]. However, I could not reliably work a BM stix meter, and their use had to be abandoned.

#### **2.11: use of "blotting paper" technique for glucose measurement.**

The second option was a "blotting paper" technique; this entails collecting drops of blood from a finger (or ear) prick onto blotting paper. The plasma glucose level is estimated by macerating standard size pieces of blood blot in standard volumes of acid and comparing the glucose concentration of this to the glucose concentration obtained from blood blots of known plasma glucose concentration [108, Mr D. Aitken, personal communication]. This method is generally used with a standard blot obtained with a glucose solution of known concentration rather than blood and gives result adequate for monitoring diabetic control [108,109]. If the patient bleeds enough, a third drop could also be used for fructosamine estimations.

The results of blood blot glucose levels (either one or the average of two) were compared to results obtained using formal venepuncture and a Technicon autoanalyser (modified Hoffman method) in diabetic outpatients (Figure 2.9).

The blotting paper method produced an average coefficient of variation from formal venous plasma glucose levels of 11.9% with no particular bias and I considered that it was unsuitable for use in the screening survey.

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Figure 2.9: table comparing blood blots versus formal random plasma glucose (mmol/l).

Subject	Spot 1	Spot 2	Technicon	Coefficient variation (%)
R.Hick	5.9	5.9	5.6	+ 5.4
C.Ward	3.0	3.0	3.7	-18.9
Bel t .2	33.5	-	27.7	+28.2
But l .1	14.4	-	12.1	+19.0
I .Hayw	5.2	5.5	5.6	- 4.5
V.Wils	3.9	4.1	4.9	-18.4
M.Danv	4.8	4.6	5.6	-16.1
Mat t .2	8.7	-	8.2	+ 6.1
Mat t .1	11.2	-	9.1	+23.1
Arms .2	16.2	-	15.6	+ 3.8
Arms .1	18.1	-	16.2	+11.7
G.Mar t	4.6	5.3	5.6	-11.6
M.Tuit	5.0	6.3	5.6	+ 0.9
But l .2	13.1	-	12.6	+ 4.0
Gray .2	18.7	-	17.1	+ 9.4
J. John	5.3	4.9	7.0	-27.1
V.Tran	6.8	5.9	6.4	- 0.8
C.Heat	8.0	8.9	9.5	- 5.8

#### 2.12: use of capillary tubes for glucose measurement.

The third option was to collect blood into Sarstedt capillary tubes. The word capillary here refers to the source of the blood rather than to any capillary action of the tubes to draw up the drop of blood. Although the Beckman analyser can perform two to three glucose estimations on a full capillary tube of blood, I experienced great difficulty in getting the tubes one third full despite vigorously bleeding fingers and ears (personal observations).

#### 2.13: the use of formal venepuncture for glucose measurement.

The final option was to perform a formal venepuncture. This was more invasive than a finger prick, and used more equipment. It was not, however, excessively time consuming compared to the finger prick techniques, and in practice nearly all patients found it acceptable. The great advantage was that a larger volume of blood was obtained allowing a spare glucose specimen to be obtained as a safeguard against accident, and the blood glucose estimation could be repeated many times on the Beckman analyser; blood samples for biochemical and

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haematological analysis could also be taken. It was interesting to note that in the NHANES II survey [20] results for 3872 GTTs were obtained, but a further 98 GTTs had no result due to loss and breakage of the blood specimens.

One final reason for using venous plasma for glucose estimations is that the original work defining the blood glucose level above which diabetic specific complications were likely used venous plasma specimens [85,87,88,89].

Thus it was decided to use the final option since it offered greater precision in glucose level estimation, and allowed other blood estimations to be performed; it was also comparable with many other studies and was the method recommended by the NDDG [50].

#### **2.14: confirmation of the diagnosis of diabetes and IGT.**

Both the NDDG and WHO criteria [50,51] for diabetes suggest that a person should have not only an abnormal GTT, but also diabetic symptoms or a further abnormal blood glucose to make the diagnosis of diabetes. Apart from Jarrett and Keen in follow up of IGT subjects from Bedford and Whitehall [90,110,111], and McLarty and Swai in Tanzania [112], few investigators perform the second GTT. Because the GTT can be a very variable test, diagnostic criteria using two features are necessary; individual coefficients of variation of the GTT may be approximately 25% [100,113]. Although the Islington survey [75] found even greater variation, their second GTTs were performed up to one year after the initial GTT. A recent editorial has also made this point [114] that the variability of the oral glucose tolerance test should be realised. It has also been suggested that in some populations, a high initial GTT result may be due to the stress of the test rather than the variability of the test (for whatever reason) or impairment of glucose homeostasis [112], since GTT results in some subjects decreased dramatically on the second GTT.

There is also a problem with IGT; some believe that if a subject has a 2 h value in the IGT range, then a fasting blood glucose that is not in the diabetic range is necessary to confirm the diagnosis of IGT [115]. The WHO criteria [51,84] can

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be interpreted this way, but a recent review by R Jarrett did not state why this was felt necessary [116]. They can also be interpreted that the fasting value is unnecessary. In the Coventry community survey [76], no one with IGT 2 h values had diabetic fasting values [D Simmons, personal communication], and the same applied in Israel [117]. Thus I believe that the fasting blood glucose level is superfluous in defining IGT.

My interpretation of the WHO criteria left a small group of asymptomatic people with 2 h blood glucose values initially in the diabetic range, but on retesting they were below the diabetic range; these were labelled as IGT although in other studies they would be labelled diabetic. These subjects would have benefited from the category of previous abnormality of glucose tolerance (PAGT) in the National Diabetes Data Group criteria [50], which is interesting because overall the NDDG criteria leave many subjects as unclassified [23,118]; although subjects with PAGT have an increased risk of non-specific diabetic complications, their risk of progression to diabetes and specific complications is not known [50].

#### **2.15: the definition of elderly.**

The final problem is that the definition of elderly is variable. The WHO and United Nations define "elderly" as over 60 years, and "old" as over 80 years [32]; Index Medicus defines "aged" as over 65, and over 80 is classified as "aged over 80"; the government classifies pensionable as over 65 years for men, for reasons discussed in Chapter 1.

Thus, not surprisingly, the age strata used by different investigators often differ, but I will follow government guidelines and examine subjects aged 65 and over.



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### 2.16: the diabetes screening survey method.

A diabetes screening survey was therefore performed to define total prevalence in a sample representative of British elderly, using the town of Melton Mowbray, and environs. Melton is a Leicestershire market town which has many industries including iron and steel works, agriculture, and pork pie, pet food and Stilton cheese production. The elderly population is almost totally North European Caucasian. It has both rural and urban environments and a stable population. Data from the Office of Population Censuses and Surveys' 1971 census shows that the Standardised Mortality Ratio of the local inhabitants is 0.98 (95% CI 0.93 to 1.04), and the age and social class structure of the population is similar to that of England and Wales (Figures 2.10, 2.11) [119]; More recent OPCS data show that in 1990 the age structure was again similar to the rest of the UK [120] (Figure 2.10), and there was no overall change in Leicestershire population numbers due to migration with a very low migration rate of 0.75% in subjects aged 60 or more.

Figure 2.10: table showing age groups as percentage of whole population in Melton and UK (%).

	Over 75 Years	Over 65 Male	Over 60 Female
1971:			
Melton Mowbray	4.4	4.3	9.7
England & Wales	4.8	5.1	11.3
1990:			
Melton Mowbray	6.7	6.4	11.8
England & Wales	7.0	6.4	12.0

Figure 2.11: table showing social class as percentage of whole population of Melton and UK (%) in 1971.

Social Class	Melton Mowbray	Great Britain
1	6	5
2	14	20
3	52	50
4	20	18
5	9	7

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All the patients attend one general practice which maintains an accurate computerised age/sex register, and a register of diabetic patients derived from General Practitioner (GP) and Diabetic Health Visitor records. This age/sex register was set up in 1980 in conjunction with the Leicester University department of Community Health [121]; the register was based on GP records, but these were checked by field workers whilst creating the register, and during several surveys of elderly people. The practice staff check the patients' details whenever the patients attend, and in this area 80% of elderly people visit their GP each year [121].

Local residents had participated in several previous surveys, and I hoped that this would aid recruitment; the study area was also geographically convenient for research based in Leicester.

The sample drawn from the age/sex register consisted of all residents who would be 66, 71, 76, 81, and 86 years old on their next birthday, and who were alive in August 1987 (ie everyone aged 65, 70, 75, 80 and 85); the fieldwork of the survey took approximately one year to complete. Known diabetic patients were identified from a diabetes register and their records inspected to confirm the diagnosis, and to confirm that they were resident in the area when the sample was drawn.

The computerised list of subjects was ordered by post code (by the computer); each post code contains approximately 20 home addresses, and thus the subjects could easily be approached by area. Interestingly, I surveyed the Post Office official responsible for organising the post codes, and found him to be diabetic.

Subjects were sent a letter outlining the study, and were then contacted by telephone or personally to organise the modified oral glucose tolerance test (MOGTT), if alive and willing. The MOGTTs were performed from August 1987 to August 1988. The patients fasted overnight and then drank 388 ml of substantially degassed Lucozade, equivalent to 75 g of anhydrous glucose. A single 20 ml venous blood sample was taken 2 h later from each subject and placed in two fluoride oxalate tubes, an EDTA tube and a plain clotted tube; the

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specimen was kept cool at approximately 4°C, spun down within 4 h, and the plasma frozen for later glucose measurement on a Beckman glucose analyser 2 (Beckman Instruments, Galway, Eire) using the glucose oxidase method. The MOGTTs were done either by myself, or my co-fieldworker, Mrs M Bodington.

The results were interpreted according to 1985 WHO [51] criteria; subjects with an initial MOGTT value of 11.1 mmol/l or more were retested within seven days. If the second value was above 11.1 mmol/l, the subject was labelled diabetic, and if the second value was below 11.1 mmol/l, the patient was labelled as having IGT.

Those who refused the MOGTT had their medical records at the general practice and local hospitals and their hospital biochemistry records examined for evidence of glucose tolerance status. Some subjects could not be contacted due to moving house or death and a history was then obtained from the neighbours about the subjects' fate and whether they were resident in the area when our sample was drawn.

Many spouses, and some neighbours also wished to be tested, and their results were recorded separately.

#### **2.17: results of diabetes screening survey; subjects surveyed and known diabetic subjects.**

Of the initial subject computer list, 63 had died or migrated before August 1987, from 3 days to 30 years previously and included one person with known diabetes; none of these subjects are considered further in this analysis.

From the remaining sample of 861 (365 male), 48 were known to have diabetes under medical follow-up, although 15 of these were identified when offered an MOGTT, rather than from the diabetic register, and 5 of these (FSw, FRa, IOI, ERo, RRa) were diagnosed by other physicians during the course of the survey (Figure 2.12). Formal follow up was by GP, or Diabetologist (Diab), but there were no formal follow up plans for some patients including one subject with IDDM (JBa, 70, M), and many subjects had not had a glycosylated haemoglobin

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measured within the last year (Figure 2.12). It is interesting to note the large usage of the long acting sulphonylureas, glibenclamide (Glib), and chlorpropamide (Chlorp) (Figure 2.12).

A further 4 subjects (JRo, WMo, RRa, TSt aged 65, 70, 75 and 85 years) had previous plasma glucose levels diagnostic of diabetes, but were not aware of their problem and their medical records did not contain the diagnosis of diabetes. Thus there were 52 subjects (24 male) with previously diagnosed diabetes, of whom 7 (13%) were insulin dependent (IDDM) and 10 (19%) were insulin treated. These figures for insulin treatment are very similar to those from Oxford (21.8%; 95% CI 16.2-28.3) [41], Nottingham (13%; 95% CI 7.3-21.6) [40], and Poole (10%; 95% CI 3.3-21.8) [121a].

Interestingly one subject (FSt, 70, M) was diagnosed diabetic by his GP less than one year before the start of the survey, but he had had diagnostically elevated blood glucose levels 7 years before the start of the survey. Another subject (RCo, 75, M) had had diet controlled diabetes for 27 years which some would label as "mild", but he needed laser photocoagulation for sight threatening retinopathy.

There were three subjects wrongly labelled as diabetic; one male aged 70 had normal glucose tolerance and a low renal threshold previously shown on GTT, one male aged 75 was normal on GTT performed after a one off high blood glucose level, and one female aged 80 (later found to be normal on testing) was on the diabetic register due to a clerical error since she had the same name as a genuine known diabetic.

2 subjects were Asian Caucasian (1 refused MOGTT, 1 normal MOGTT), and all other 859 subjects were white Caucasian. 2 subjects were residents of a convent, and 5 were in a Part 3 home; all these subjects received an MOGTT. 1 subject was in geriatric continuing care, one was in long stay psychiatric care, and one Part 3 resident died; these subjects were not tested. All remaining residents (known diabetic patients, and those who were or were not tested) were resident in their own homes

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Figure 2.12: details of known diabetic subjects in Melton Survey.

Subject	Age	Sex	Type	Duration	Treatment	Care	HbA1
CCo	65	M	1	12y	Insulin	Diab	5.3
HJo	65	M	2	4y	Glib	GP	-
ESc	65	M	2	2y	Glib	GP	-
MSz	65	F	2	3y	Glib	GP	-
PJa	65	F	1	32y	Insulin	Diab	-
MFo	65	F	2	6y	Diet	GP	-
VBa	65	F	2	2y	Diet	GP	10.3
EMa	65	F	2	7m	Glib	GP	14.6
TFi	70	M	1	24y	Insulin	GP	12.1
AWe	70	M	2	7y	Glib+Met	GP	-
FSi	70	M	2	7y	Tolb	GP	-
RRo	70	M	2	2y	Metformin	GP	7.0
WPr	70	M	2	7y	Metformin	Diab	-
JBa	70	M	1	22y	Insulin	-	-
EAt	70	F	2	15y	Insulin	Diab	8.6
EMa	70	F	2	4y	Glib	Diab	11.1
IMa	70	F	2	11y	Insulin	GP	9.7
FMa	70	F	2	1y	Glib	GP	8.7
IHa	70	F	1	3y	Insulin	Diab	-
FSw	70	F	2	-1m	Diet	GP	-
MKe	70	F	2	8y	Insulin	GP	12.2
JSp	70	F	2	1m	Metformin	Diab	7.8
ESh	70	F	2	8y	Chlorp	GP	14.5
NCI	70	F	2	3m	Glib	GP	-
FRa	75	M	2	-1m	Diet	GP	-
RCO	75	M	2	23y	Diet	Diab	4.8
IOI	75	M	2	-1m	Diet	Diab	3.7
SYo	75	M	2	3y	Diet	Diab	-
GTy	75	M	2	2y	Glib	GP	5.1
ANe	75	F	2	2y	Diet	GP	-
EPi	75	F	2	2y	Diet	GP	-
LBu	75	F	2	1y	Diet	GP	-
ERo	75	F	2	-1m	Glib	GP	-
ALe	75	F	2	8m	Glib	GP	8.0
LMo	75	F	2	7y	Chlorp	GP	-
EMa	75	M	2	1y	Diet	-	-
LFo	75	M	1	36y	Insulin	Diab	-
DJa	75	F	2	4y	Glib	GP	9.3
GPe	75	F	1	53y	Insulin	-	-
CSh	75	F	2	1y	Glib	GP	-
KKo	80	M	2	4y	Metformin	GP	-
CCh	80	M	2	4m	Glib	GP	-
AAa	80	M	2	5y	Glib	GP	-
ENa	80	M	2	6y	Diet	GP	-
DEI	80	F	2	8m	Diet	GP	-
BPh	80	F	2	?	Diet	GP	-
DGI	85	F	2	16y	Diet	GP	-
JCo	85	M	2	7m	Diet	GP	-
TSi	85	M	2	4m	**	-	-
RRa	75	M	2	-4m	**	-	-
WMo	70	M	2	1y	**	-	-
JRo	65	F	2	3m	**	-	-

Note: \*\* some subjects had diagnostic plasma glucose levels, but had not been formally diagnosed as diabetic previously.

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#### 2.18: results of subjects tested by MOGTT.

An MOGTT was performed on 583 subjects from the main sample; the majority of the 226 not tested were not tested due to refusal. A further 15 subjects were not tested because they were diabetic, but not on the diabetic register; these included:-

- a. 2 subjects who initially agreed to a GTT, but who then asked if they should continue their sulphonylurea.
- b. 9 subjects who told us to go away, and whose records revealed that they were under medical follow up for diabetes.
- c. 4 subjects who told us to go away, and whose records revealed at least 2 plasma glucose levels diagnostic of diabetes, but they had not had the diagnosis of diabetes formally made.

159 spouses and neighbours were also tested, since if the test was being offered to the main subject on the grounds of detecting a serious health threat, it was unethical not to test any other elderly subject present; data from this extra group were kept separate.

Most subjects with a MOGTT result of 11.1 mmol/l or more were diabetic on retesting; some had classical diabetic symptoms. Three subjects had initially high MOGTT results but on repeat testing had levels below 11.1 mmol/l; 2 subjects were on the main volunteer list and on retesting one had a result of 7.9 mmol/l (EJo, 75, M), and the other had a level of 5.8 mmol/l (LPh, 70, F); one spouse had an elevated first MOGTT, but on retesting attained 10.5 mmol/l (LCI, 68, M).

Figure 2.13 gives details of the subjects whose initial glucose level was more than 11.1 mmol/l, including duration of any symptoms, and final diagnosis

The diagnosis of diabetes was by repeat MOGTT in all except two cases (FBo, LWa) with classical symptoms. In subjects ending up with IGT, all had MOGTT results less than 12.8 mmol/l; one could assume that a subject with a MOGTT result of 13 mmol/l or more was diabetic; however, this is in subjects with no acute illnesses and cannot be applied to acutely ill subjects with a raised blood glucose level. Interestingly, data from Pima Indians has just been re-examined [121b]; from the bimodal distribution of GTT results obtained, the antimode was

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12.6 mmol/l, and subjects with GTT results below this did not go on to develop retinopathy. Thus, perhaps, in well subjects, a higher GTT cut-off should be considered.

Figure 2.13: table of features of subjects with initial MOGTT result greater than 11.1 mmol/l (main sample and spouses).

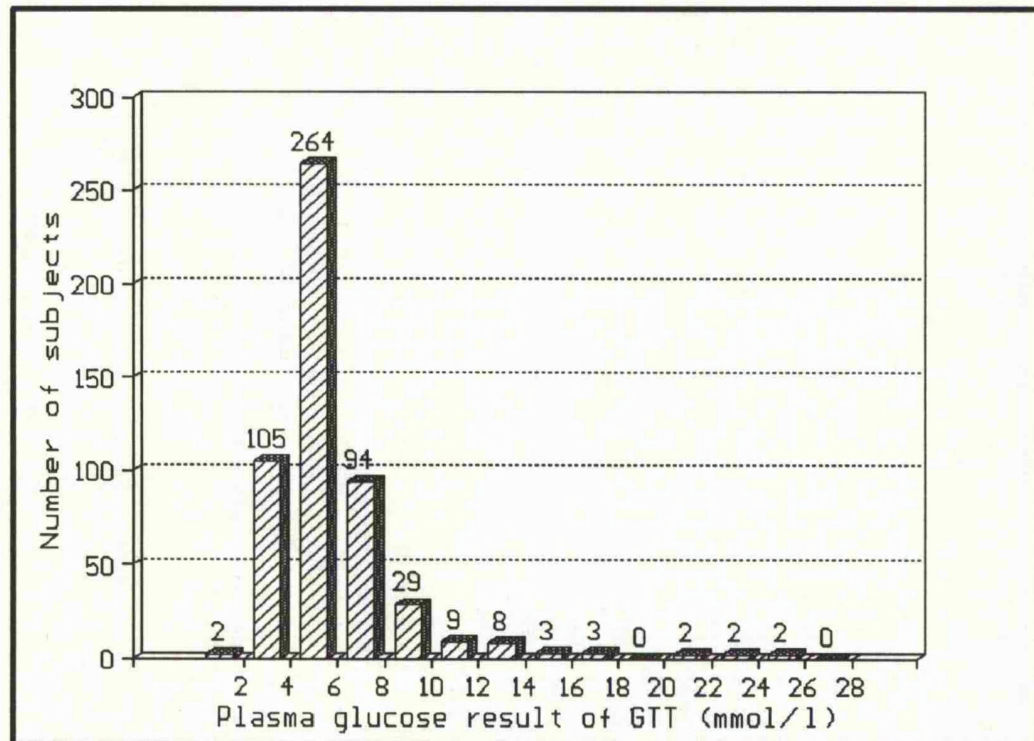
Name	No	Age (yrs)	Sex	Initial MOGTT result	Weeks of symptoms	Type of subject	Final diagnosis
THu	1124	65	M	14.9	0	V	DM
CS t	1108	65	M	22.6	0	V	DM
MAs	1140	65	F	12.7	0	V	DM
GBu	1236	65	M	12.9	0	V	DM
GLe	1232	65	M	16.6	0	V	DM
BAs	2367	65	F	20.2	0	V	DM
LWa	1157	65	M	12.3	52	V	DM
MBu	2307	70	F	16.9	104	V	DM
LDa	2435	70	F	12.5	7	V	DM
MBa	2115	70	F	18.6	12	V	DM
ECr	2022	85	F	15.0	0	V	DM
LMc	2348	85	F	13.9	0	V	DM
AHa	2298	80	M	21.0	0	V	DM
AHo	2404	80	M	22.6	0	V	DM
TVi	2169	75	M	14.3	208	V	DM
IKc	2180	75	F	24.4	52	V	DM
HNe	2424	85	F	13.8	0	V	DM
EWr	1300	80	F	24.2	0	V	DM
TPe	2244	80	M	15.4	0	V	DM
LPh	2274	70	F	11.9	0	V	IGT
EJo	2413	75	M	12.2	0	V	IGT
DCa	1302	73	M	22.8	0	S	DM
GFr	2257	79	M	19.1	0	S	DM
FBo	1211	77	M	12.1	26	S	DM
ALo	1030	68	M	14.9	0	S	DM
RWi	1086	69	M	17.2	0	S	DM
DEl	2306	66	F	14.0	0	S	DM
LCI	1181	68	M	12.7	0	S	IGT

Note: \*\*=subject refused further examination  
M=male; F=female; V=main list subject; S=spouse etc; DM=diabetic; IGT=impaired glucose tolerance.

The plasma glucose results obtained from the 583 MOGTTs are expressed in Figure 2.14.

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Figure 2.14: histogram of plasma glucose results of GTT.



From Figure 2.14 it is apparent that the results are skewed positively, and almost appear bimodal; unfortunately, one needs a prevalence of at least 10% in the 2nd mode to be able to prove bimodality [95]. The values are given as medians, quartiles etc (Figure 2.15) to allow for this skewness.

Figure 2.15: table of plasma glucose results of GTTs in main screening survey at different ages (mmol/l).

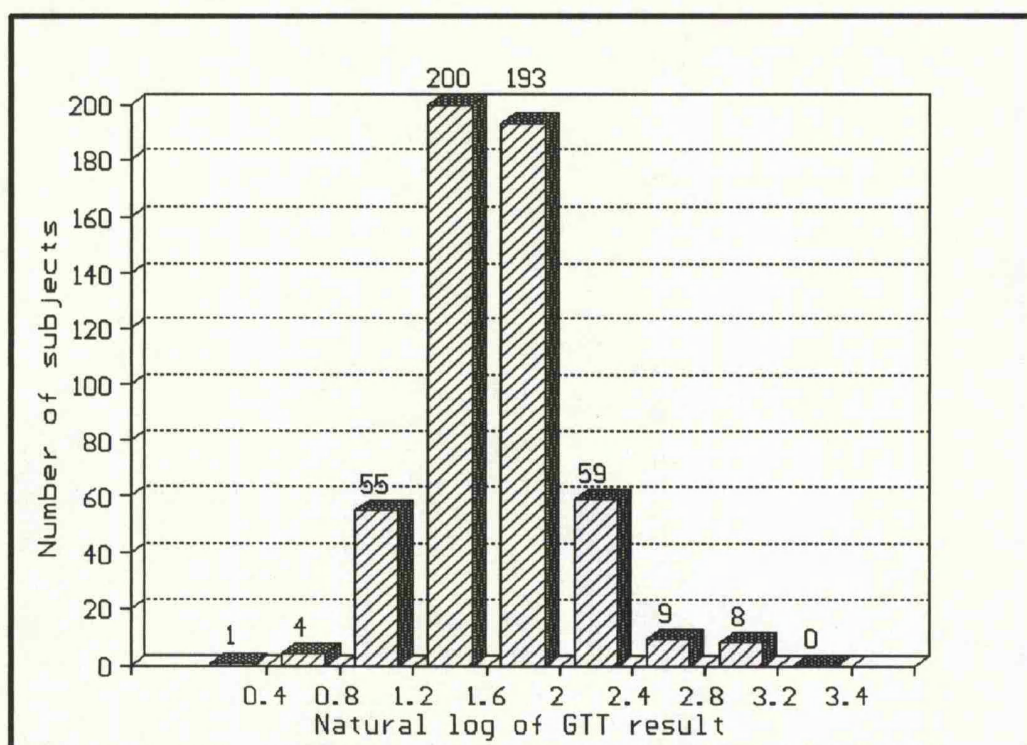
Ages:	65	70	75	80	85	Total
Number	219	134	132	66	32	583
Maximum	22.6	16.9	24.4	24.2	13.9	24.4
Upper quartile	6.2	5.9	6.3	6.4	8.2	6.2
Median	4.9	4.8	4.9	5.1	5.7	5.0
Lower quartile	4.1	4.1	3.9	4.5	4.0	4.1
Minimum	2.1	2.1	1.3	1.8	2.3	1.3



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The histogram has therefore been redrawn with an x-axis derived from the natural logarithm of the GTT result (Figure 2.16); with an x-axis interval of 0.2, the histogram still does not follow a normal distribution (distribution fitting  $\chi^2=68.7$ ;  $DF=14$ ;  $P<0.00001$ ; Shapiro-Wilk test for normality  $W=0.953$ ;  $P<0.00001$ ), and is still skewed positively, although it does appear more normally distributed than the untransformed GTT results (Figure 2.14).

Figure 2.16: histogram of plasma glucose result of GTT with log transformation.



Of the 583 subjects in the main sample who received a GTT, 19 had diabetes, 44 had Impaired Glucose Tolerance (IGT) and 520 were not abnormal; specific details for age and sex are given in Figure 2.17.

The acceptance rate for the MOGTT fell from 80% in the 65 year old subjects to 54% in the 85 year old subjects.

The MOGTT was performed on 159 spouses and neighbours aged 65 to 85 years (average age 71 years); 6 had diabetes, and 12 had IGT.

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Figure 2.17: table of results of diabetes screening survey in main sample (Numbers of Subjects).

Age: Sex	Previously diagnosed diabetes	Tested by MOGTT:			Not Tested
		Normal	IGT(*)	Diabetes	
65: male	3	86	9	5	21
65: female	6	112	5	2	33
70: male	7	59	3	0	24
70: female	10	65	4 (1)	3	26
75: male	8	42	7 (1)	1	20
75: female	9	76	5	1	36
80: male	4	23	5	3	14
80: female	2	34	0	1	25
85: male	2	5	2	0	7
85: female	1	18	4	3	20
Total	52	520	44	19	226

Note: (\*) number with initial MOGTT > 11.1 mmol/l but second MOGTT < 11.1 mmol/l, included in the number with IGT.

#### 2.19: the prevalence of diabetes in Melton.

From this sample I believe that the prevalence of previously diagnosed diabetes in Melton is 6.0% (95% CI 4.3-8.1) and the prevalence of previously undiagnosed diabetes among those not known to have diabetes is 3.3% (95% CI 2.0-5.0).

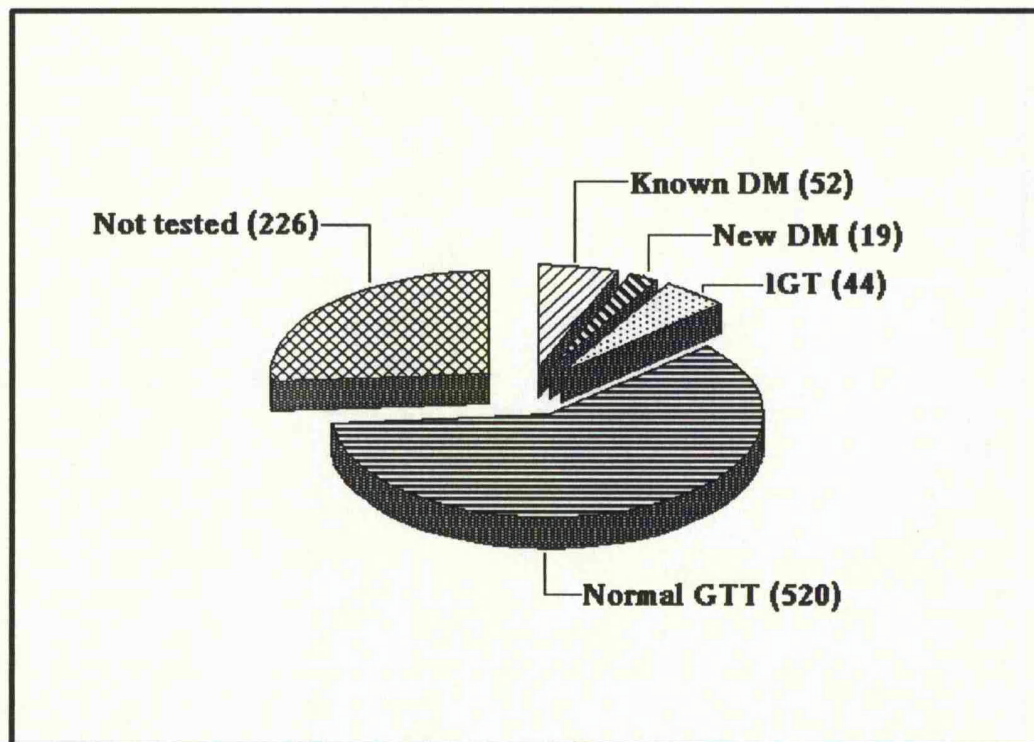
Although the spouses and neighbours were undoubtedly preselected, the prevalence of undiagnosed diabetes in this group was 3.8% (95% CI 1.4-7.9), similar to the main sample.

The socioeconomic factors in the Melton area are very similar to those of England and Wales; although the surveys in Islington [75] and Coventry [76] were not so representative of the UK, their prevalence figures were both very similar to the Melton findings. It is interesting that the results of these three surveys are so similar despite differing socioeconomic factors, since the prevalence of known diabetes has previously been shown to vary with these factors [122,123].

If one assumes that those not tested had a similar prevalence of diabetes to those tested, and this assumption will be examined in Chapter 3, then the prevalence of total diabetes (known and new) can be calculated (Figure 2.18).

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Figure 2.18: pie chart showing results of survey.



One would like to calculate the 95% confidence intervals for the estimate of total prevalence of diabetes in the study population; this is to allow for random variation within the sample of the study population causing the prevalence in the sample studied to differ from the true prevalence in the study population. One could assume that one had tested those that had not been tested and simply increase the numbers of new diabetic subjects by the proportion not tested; however, this process would give falsely precise confidence intervals since the degree of statistical uncertainty is strongly inversely related to the sample size which one had just spuriously increased [124].

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Therefore, the prevalences were calculated from the actual numbers tested with a proportion of the known diabetic subjects included:-

Number tested by GTT = n

Number not tested by GTT = t

Number new cases of diabetes = d

Number known cases of diabetes = k

Number new cases IGT = i

Prevalence of new diabetes in sample tested =  $d/n$

Prevalence of known diabetes in population sample =  $k/(n+t+k)$

Number known diabetic cases proportional to number tested, p, =  $kn/(n+t)$

Overall prevalence of total diabetes =  $(d+p)/(n+p)$

Proportion of all diabetic subjects found by testing =  $d/(d+p)$

Overall prevalence of IGT =  $i/(n+p)$

Overall prevalence of any abnormality of glucose tolerance =  $(d+p+i)/(n+p)$

On the assumption that those tested had a similar prevalence to those not tested, the age specific prevalences of total diabetes (known and new) were calculated (Figure 2.19), and the exact 95% confidence intervals were calculated using the F distribution [125].

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Figure 2.19: table of age specific prevalence of diabetes and IGT in Melton, proportion of subjects previously undiagnosed, and the calculations for these.

Age (years)	n	t	d	k	i	p	Known Diabetes $k/(n+t+k)$	New Diabetes $d/n$	Total Diabetes $(d+p)/(n+p)$	Proportion of Diabetes new $d/(d+p)$	IGT $i/(n+p)$	Total Abnormal GTT $(d+p+i)/(n+p)$
65	219	54	7	9	14	7.2	3.2 (1.5-6.0)	3.2 (1.3-6.5)	6.3 (3.5-10.3)	49 (23-76)	6.2 (3.4-10.2)	12.5 (8.4-17.4)
70	134	50	3	17	7	12.4	8.5 (5.0-13.2)	2.2 (0.5-6.4)	10.5 (6.0-16.9)	20 (4-47)	4.8 (1.9-9.6)	15.3 (9.7-21.9)
75	132	56	2	17	12	11.9	8.3 (4.9-13.0)	1.5 (0.2-5.4)	9.7 (5.4-15.7)	14 (2-43)	8.3 (4.4-14.1)	18.0 (12.1-25.3)
80	66	39	4	6	5	3.8	5.4 (2.0-11.4)	6.1 (1.7-14.8)	11.1 (4.8-21.4)	52 (16-86)	7.2 (2.4-15.9)	18.3 (10.3-29.7)
85	32	27	3	3	6	1.6	4.8 (1.0-13.5)	9.4 (2.0-25.0)	13.8 (4.6-30.4)	65 (16-97)	17.9 (6.8-34.9)	31.5 (17.4-50.5)
All ages	583	226	19	52	44	37.5	6.0 (4.3-8.1)	3.3 (2.0-5.0)	9.1 (7.0-11.9)	34 (22-47)	7.1 (5.2-9.4)	16.2 (13.4-19.4)

n = number tested by GTT.

t = number not tested by GTT, but surveyed and known diabetic subjects identified.

d = number new cases of diabetes found by GTT.

k = number known cases of diabetes.

i = number of cases of IGT found by GTT.

p = number of known diabetic cases proportional to proportion of eligible cases tested, ie  $kn/(n+t)$ .

Note: columns may not add-up due to rounding errors, and because most columns include a proportion of known diabetic subjects in the denominator, but the new diabetes column does not.

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An alternative method to obtain limits between which one is certain that the true prevalence of diabetes lies, albeit not 95% CLs, is to calculate limits on the assumption that the subjects not tested were either all diabetic or all non-diabetic [126]. Although this gives limits encompassing the true prevalence, I feel that they are too wide to be meaningful. An estimate that is close to the mark, but none the less wrong, is more use than a wide range which encompasses the correct answer [127]; for instance, at 12.05 hours the statement that the time is midday will be more use than the more correct statement that the time is somewhere between 9.00 hours and 15.00 hours. On the other hand, when the Pope's advisors told him that the Black Death had killed 1,244,434 in Germany, what they meant was that an awfully large number had died [128]. Thus wild figures and misleading statistics may be used to make one's point [129,130]; however, I would not do this. It has been noted that an understanding of basic statistics is essential in modern life [129].

The age specific prevalence increased from 65 to 85 years of age, but the confidence intervals are wide in the octogenarians making the significance of this uncertain. Certainly, the Kendall's rank correlation coefficient tau is 0.8 (2 tailed  $P=0.083$ ) for prevalence of total diabetes versus age. Examining the actual numbers of subjects with diabetes (d+p) and subjects without diabetes (n-d) for each age group revealed no evidence of a different prevalence of diabetes with age ( $\text{Chi}^2=3.834$ ,  $\text{DF}=4$ ,  $P=0.43$ ), and no trend with age ( $\text{Chi}^2$  for trend in mean scores=2.947,  $\text{DF}=1$ ,  $P=0.086$ ). Referring back to the actual blood glucose levels of the GTTs (Figure 2.15), there is a trend for the median GTT result to increase from age 65 to 85, but there is no significant difference on comparing the GTT results obtained from the two extreme age groups (Mann Whitney U test 2 tailed  $P=0.185$ ).

Examining the actual numbers of subjects with IGT (i) and subjects without IGT (n+p-i) for each age group revealed no evidence of a different prevalence of diabetes with age ( $\text{Chi}^2=7.71$ ,  $\text{DF}=4$ ,  $P=0.10$ ), and no trend with age ( $\text{Chi}^2$  for trend in mean scores=3.63,  $\text{DF}=1$ ,  $P=0.057$ ).

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However, examining the actual numbers of subjects with any abnormality of glucose intolerance (d+p+i) and subjects with normal glucose tolerance (n-d-i) for each age group revealed no evidence of a different prevalence of diabetes with age ( $\chi^2=8.85$ ,  $DF=4$ ,  $P=0.065$ ), but there was a trend with age ( $\chi^2$  for trend in mean scores=7.12,  $DF=1$ ,  $P=0.0076$ ).

Thus there does not seem to be any change in the prevalence of diabetes in the Melton sample from age 65 to age 85. However, I may be making a type 2 error here since "any abnormality of GTT" did have a trend to increase with age, and if one repeats the calculations having doubled the numbers, then the  $\chi^2$  trend in mean scores is significant ( $\chi^2=5.89$ ,  $DF=1$ ,  $P=0.015$ ), and comparing 65 to 85 year olds with a 2 tailed Fisher's exact P is also significant (0.041). Thus a further study to compare glucose tolerance in 65 and 85 year old subjects with larger sample size and even more strenuous attempts to increase recruitment would be interesting.

It is said that in systems undergoing age related multifactorial degeneration, the variance of the measurement increases with age [1]. Thus the variances of the natural logarithm transformed GTT results were calculated with their 95% confidence intervals [131] (Figure 2.20), since these were closer to a Gaussian distribution than the untransformed GTT result.

Figure 2.20: table of variance of logarithm transformed GTT result with age.

Ages :	65	70	75	80	85	Total
Variance	0.16	0.11	0.16	0.18	0.24	0.15
95% CI	.13-.20	.09-.14	.12-.20	.13-.26	.14-.40	

Although the variance does increase at age 85, the variances for each age group are similar with overlapping confidence intervals. Also the F ratio of the variances [131] showed no significant difference ( $p>0.1$ ) when comparing the 65 to 85 year groups and comparing each group to the total group. Thus the variance of the observation does not increase with age in this study; possible explanations

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would include a type two error, the underlying concept of increasing variance with ageing being incorrect, or that the variance has plateaued in the sample studied. The final explanation is most attractive since data from the NHANES II [20] study show increasing variance with age from 45 to 75 (Figure 2.21).

Figure 2.21: spread of results from Melton and NHANES II with age.

Age (years)	GTT results at percentiles of distribution (mmol/l)		
	5th	50th	95th
Melton			
65	2.96	4.98	10.68
70	2.90	4.80	9.16
75	2.67	4.90	9.12
80	3.10	5.10	18.76
85	2.43	5.65	13.85
NHANES II			
20-44	3.50	5.33	8.44
45-64	3.61	6.05	11.77
65-74	4.00	6.77	13.38

If one makes the assumption that all not tested were either all diabetic or all not diabetic, then the range for total diabetes for the total population is 8.24-34.5%; the lower limit is not greatly different from the lower limit calculated above, but the upper limit at approximately one third of the population would seem to be excessively high. Thus the lower limits obtained by whichever method show that diabetes is more common than usually appreciated [15-17].

#### 2.20: sex difference in diabetes prevalence.

Of the male subjects on the main survey list, 24 were known to be diabetic and 336 were not known to be diabetic (prevalence=6.7%, 95% CI 4.3-9.8); of the female subjects, 28 were known to be diabetic and 473 were not known to be diabetic (prevalence=5.6%, 95% CI 3.7-8.0). There is therefore no sex difference in prevalence of known diabetes in the elderly of Melton (2 tailed Fisher's exact P=0.563).



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Of these male subjects who received a GTT, 9 were diabetic, 26 had IGT, and 215 were normal, ie 241 were not diabetic; of the female subjects tested, 10 were diabetic, 18 had IGT, and 305 were normal (Figure 2.22).

There is therefore no sex difference in prevalence of previously undiagnosed diabetes in Melton (2 tailed Fisher's exact  $P=0.815$ ).

Figure 2.22: table of results of GTTs in Melton by sex (numbers of subjects).

	Male	Female
Diabetic GTT	9	10
Prevalence (%)	3.6	3.0
& 95% CI	1.7-6.7	1.4-5.5
IGT GTT	26	18
Prevalence (%)	10.4	5.4
& 95% CI	6.9-14.9	3.2-8.4
Normal GTT	215	305
Prevalence (%)	86	92
& 95% CI	81-90	88-94

There is however a difference between the two sexes when examining IGT independently; IGT is more common in males (2 tailed Fisher's exact  $P=0.0268$ , comparing IGT to all non-IGT subjects). A few other studies have documented the sex specific IGT rates and generally these are the same for male and female subjects [20, 25,76]; the Islington study [75] suggested that IGT was less common in elderly men (prevalence 3.4%; 95% CI 1.3-7.3) than in elderly women (prevalence 8.5%; 95% CI 5.3-12.7), but this was not significant (2 tailed Fisher's exact  $P=0.0669$ ). I would like to find some confirmatory evidence of an increase in IGT in elderly men, which might contribute to the earlier mortality of elderly men from vascular disease [131a]. However, confirmatory evidence is not available.

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#### 2.21: effect of urbanisation on diabetes prevalence.

One can also compare the prevalence of diabetes for urban and rural areas; I classified Melton Mowbray itself as urban, and the surrounding villages as rural (Figure 2.23). There is no difference in prevalence of known and previously undiagnosed diabetes for the different areas (2 tailed Fisher's exact  $P>0.1$ ). Other surveys have shown a difference [53,132]; although I have small figures and may be making a type 2 error, it is likely that there is no difference in the Melton area because urban and rural environments are so similar, unlike the third world countries where this urban/rural split occurs.

Figure 2.23: table comparing diabetes in urban and rural areas of Melton (numbers of subjects).

	Urban	Rural
Known DM	39	13
Not known DM	653	156
Prevalence (%)	5.64	7.69
known DM & 95% CI	4.0-7.6	4.2-12.8
Diabetic GTT	16	3
Non-diabetic GTT	460	104
Prevalence (%)	3.36	2.80
unknown DM & 95% CI	5.4-1.9	0.6-8.0

Note: DM=diabetes.

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### Diabetes in the elderly.

#### **2.22: misdiagnosis of diabetes in Melton.**

Three subjects had an inappropriate diagnosis of diabetes, as documented in Section 2.17. This is not remarkable. When NHANES II examined the prevalence of diabetes across the USA [20], of 100 self reported non-insulin dependent diabetic subjects, 19 (on diet alone) were completely normal on performing a glucose tolerance test (GTT). There are three possible reasons for this paradox [133]:-

1. The subjects improved their glucose intolerance by weight reduction etc.
2. The diagnosis was made prior to 1979, and would have been labelled as impaired glucose tolerance today [50,51].
3. The subjects were not properly classified initially, perhaps merely having a low renal threshold.

The converse is, of course, that if one asks subjects if they are diabetic, some with a previous diagnosis of diabetes deny it, about 16% in the Southall survey [15].

#### **2.23: the increase in prevalence of known diabetes.**

The prevalence of diagnosed diabetes in the elderly of Melton was 6.0% which is slightly lower than in Leicester city, similar to Coventry, but still higher than in Oxford, Poole, and Southall; it could be a geographical variation in true prevalence of diabetes, but it could also be due to the Leicestershire diabetic health visitors not allowing known diabetic subjects to be forgotten. However, even in Melton, there were patients with previously diagnosed diabetes that had not been told the diagnosis, and neither had their health visitors.

There has also been a considerable increase in the prevalence of known diabetes in the elderly over the last 3 decades (Figure 2.24). I suspect that this reflects greater ascertainment of the actual number of diabetic subjects due to increasing use of multi-channel biochemical analysers, increasing public awareness and increased medical testing.

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Figure 2.24: table showing the prevalence of known diabetes in UK.

Study	Year	Age	Prevalence (%)	95% CI	Reference
Ibstock	1958	65+	2.7	1.35-4.77	73
Newcastle	1959	60+	1.20	0.25-3.47	69
Halstead	1959	60+	1.87	1.19-2.79	68
Forfar	1962	65+	2.24	1.54-3.15	72
Edinburgh	1968	60+	1.92	1.83-2.01	57
Oxford	1982	60+	3.04	2.69-3.43	17
Poole	1983	60+	2.75	2.53-2.98	17
Poole	1983	65+	3.11	2.84-3.39	16
Southall	1984	60+	3.34	2.92-3.81	17
Southall	1984	65+	3.72	3.21-4.28	15
Leicester	1984	65+	10.53	9.79-11.31	53
Maidenhead	1987	60+	3.80	3.13-4.57	61
Coventry	1987	60-79	4.43	2.94-6.39	76
Melton	1987	65-85	6.04	4.54-7.84	-
Ipswich	1990	65-70	3.67	2.13-5.76	134

However, one wonders if there may actually be more diabetic subjects in total for several reasons:-

1. The advent of insulin means that young subjects with insulin dependent diabetes mellitus (IDDM) can survive to become elderly.
2. IDDM is becoming more common in younger subjects [135].
3. Diabetes is associated with hypertension [136], and now there is effective treatment for hypertension [137].
4. There is a suggestion that diabetic subjects gain more from interventions to decrease cardiovascular disease risk [138], and there is some evidence that the mortality from ischaemic heart disease might be falling in diabetic subjects [139].
5. One would expect diabetic subjects to benefit from the health gains due to improved socioeconomic and medical factors like everyone else [5].
6. NIDDM could conceivably be getting more common as population becomes more affluent [132].

Even if there are more diabetic elderly people, this might very well not increase the prevalence, since the total number of elderly has risen greatly this century (see Chapter 1).

It is very difficult to ascertain the overall prevalence of diabetes in the earlier screening surveys since they generally prescreened with urinalysis, and did not

### Diabetes in the elderly.

recognise IGT as such. However, it is worth trying to make some comparisons with Melton and Coventry [76] whose overall prevalences were 9.3% (95% CI=7.0-11.9) and 7.03% (95% CI=4.7-10.1), respectively in 1987.

Following the Bedford study [66], and anticipating the introduction of IGT by several years, Butterfield and coauthors estimated that prescreening with urinalysis, and then performing a GTT with an 11.1 mmol/l cut off for diabetes probably missed half the diabetic subjects who were not already known [140]; since they also point out that the renal threshold rises with age, one would expect more elderly diabetic subjects to be missed. In the Melton survey, I found that only half the newly diagnosed diabetic subjects had glycosuria (see Section 4.10). It is important to note that in all the studies I am about to consider, urinalysis was performed using a glucose oxidase reagent strip (generally Clinistix), rather than the modified Benedict's test (Clinitest tablets) which are less sensitive [58,69]. In the Ibstock survey [75], there were 408 subjects aged 65 or more; 11 were known to be diabetic. Overall there was an 85% acceptance rate for prescreening urinalysis and subsequent GTT if positive; this revealed 9 latent diabetic subjects aged 65 or more who would be classed as diabetic by today's guidelines, and six intermediate subjects who today would be labelled as IGT. If one assumes a high recruitment rate in the elderly, and accepts that half the undiagnosed diabetic subjects were missed in the survey [140], then the population of 408 would contain 29 diabetic subjects giving a prevalence of 7.1% (95% CI=4.8-10.1). Unfortunately, the Newcastle, Halstead and Forfar studies [69,68,71,72] used non-standard 2 hour glucose values of 100 mg%, 100 mg% and 140 mg% respectively to diagnose diabetes and did not give further details of subjects with higher values, making further interpretation difficult.

However, the Birmingham studies of 1962/63 are well documented. The 1962 survey [58] prescreened with urinalysis and tested those with glycosuria by a GTT; this survey was followed in 1963 [70] by a study testing those that did not have glycosuria on the previous survey. It is unfortunate that many histograms are used and results are expressed as "percentages of the general population" rather

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### The prevalence of diabetes.

than simple tables of figures, but their findings can be reinterpreted by recent WHO criteria [51].

The 1963 report [70] shows a histogram of diabetes prevalence (known, found after urinalysis, and found after "random GTT") and the 1962 report [58] also has a histogram of known diabetes prevalence from which the prevalence of known diabetes can be directly read (subjects aged 70 or over male prevalence=1.8%, female prevalence=2.2%); I will accept these as true figures for known diabetes post IGT introduction, although in a population with a continuous surveillance for diabetes, the introduction of IGT deleted 16% of previously known diabetic subjects [59].

One can also find that from the 1962 report [58] that GTTs in subjects chosen by positive glycosuria revealed prevalences of newly diagnosed diabetes of 2.1% in females and 2.9% in males aged 70 or over in the general population; however, the 1962 report [58] showed that over all ages only 52 of their 127 diabetic subjects would be classed as diabetic today so that these figures for post urinalysis diabetes should be adjusted proportionally (male prevalence=1.2%, female prevalence=0.86%).

From the 1963 report [70] one can also see that "random GTT" testing by which the authors mean GTTs in subjects without glycosuria, gives prevalences for diabetes revealed by testing subjects without glycosuria of 15.8% in males and 30% in females in the elderly general population using the criteria of that time; however, this report also shows that in subjects aged 70 or more, only 5 of 18 diabetic subjects would now be thought diabetic, giving adjusted prevalences of 4.4% for males and 8.3% for females. Interestingly, of the 46 elderly subjects without glycosuria 6 (13%) had diabetes by today's standards on testing [70]; these subjects found by "random" GTTs are more numerous than one would expect from the re-examination of the Bedford data of all ages [140], but I am sure that they are appropriate due to the higher renal threshold in the elderly [140].

One can simply total the prevalences for diabetes in Birmingham (known, revealed by testing subjects with glycosuria, and revealed by testing subjects

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### Diabetes in the elderly.

without glycosuria) to give prevalences in males of 7.4% and females 11.4% in subjects aged 70 or more.

I accept that the above calculations may be imprecise, but they are the best possible with available data; they do suggest that the prevalence of diabetes 25-30 years ago in Istock and Birmingham does fall within the 95% confidence intervals of the Melton and Coventry studies and I believe that the overall prevalence of diabetes in the elderly has not changed a great deal in the last three decades.

#### 2.24: why is the prevalence of diabetes different in different Euroid populations?

It is interesting that the prevalence in the 3 UK screening surveys is consistently lower than in other Euroid populations. It is impossible to identify all the factors responsible for this from the present survey, but the contribution of body weight can be briefly assessed.

Figure 2.25: table of average Body Mass Index and prevalence of diabetes for male subjects aged 65 to 75 in different studies.

Study	Ref	Age	Diabetes rate (%)	BMI (Kg/m <sup>2</sup> )
Melton UK	-	65-75	8.9	26.42
Fredericia Denmark	22	60-74	7.2	25.47
Kuopio Finland	25	65-74	17.8	26.60
East/West Finland	26	65-74	29.8	26.18
Gothenburg Sweden	27	67	10.8	25.35

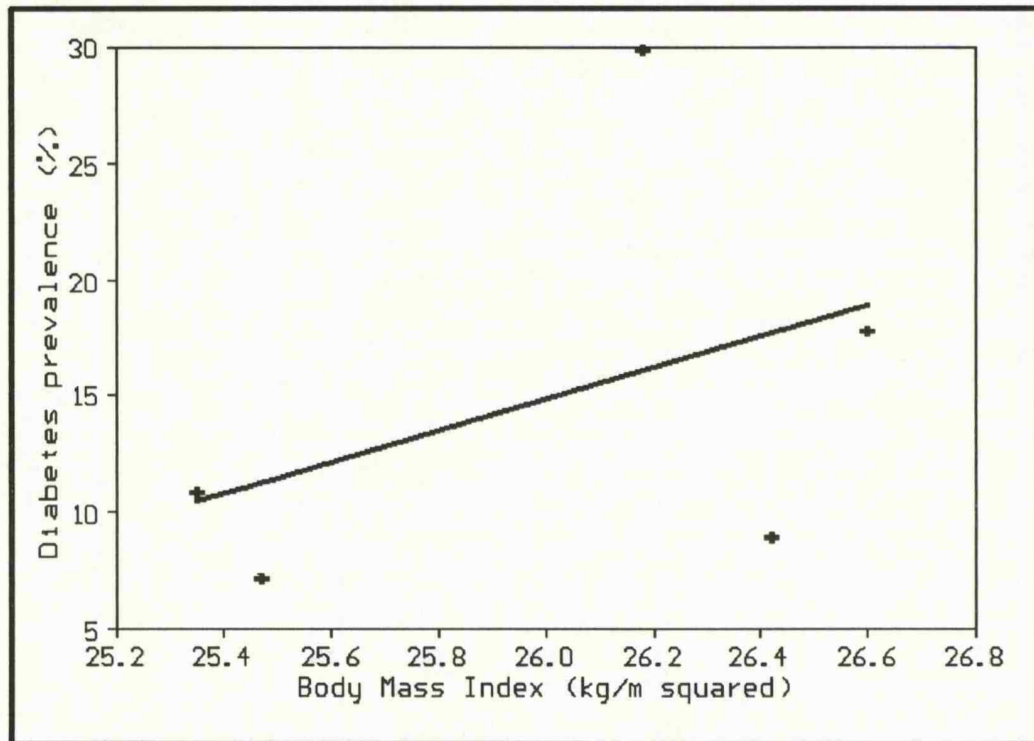
From data in Chapter 5, the body mass index (BMI) was calculated for all male subjects aged 65 to 75 in the Melton survey, assuming that the known diabetic subjects had similar weights to the newly diagnosed diabetic subjects; these

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subjects were chosen since they are well represented in the literature (Figure 2.25).

The graph of diabetes prevalence versus BMI is given in Figure 2.26.

Figure 2.26: graph showing diabetes prevalence versus Body Mass Index.



Although Figure 2.26 suggests that there is a correlation between prevalence of diabetes and BMI in these different populations, there is not (Kendall's rank correlation coefficient=0.2; 1 tailed P=0.41), and this is not altered by deleting the East and West Finland study [26] from the calculations; this is despite the well known association of diabetes and obesity within populations [20,25]; this international lack of association could be a type 2 error or it could reflect that other factors are also very important in determining diabetes prevalence. The Kuopio survey [25] in multiple regression analysis found that obesity explained only 10% of the variance in glucose level, suggesting that other factors such as genetic factors [20,25,141], exercise [27,142], and height and intrauterine development [143,144] are likely to be important in determining prevalence of NIDDM. Other factors known to influence diabetes incidence in young people



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may be relevant such as nutrition and material deprivation in childhood [145,146], diet [147], and environmental factors [148]; there are probably other factors which have not yet been identified.

#### 2.25: conclusions.

The determination of the prevalence of diabetes is fraught with problems when examining either known diabetic subjects or performing a screening survey. Very few surveys use the same methods making comparisons between surveys difficult at times. Screening surveys should use the venous plasma glucose level 2 hours after a 75 g glucose load and 1985 WHO criteria. There have been no previous surveys focusing on average elderly British people and their prevalence of diabetes. On screening the elderly of Melton for diabetes, 6.0% were known to have diabetes, and 3.3% of subjects tested were found to have previously undiagnosed diabetes, giving an overall prevalence of diabetes of 9.1%. There was no change in prevalence of diabetes with sex but IGT was more common in males (prevalence=10.4%) than females (prevalence=5.4%). The prevalence of diabetes did increase as the subjects were older eg prevalence at 65 years was 6.3% and at 85 years was 13.8%, but the significance of this is uncertain, probably due to the small sample size.

Two other screening surveys in the UK in Coventry and Islington have yielded similar prevalences in the elderly and these rates are fortunately lower than in many other European populations; the reason for this is uncertain.

It appears that the increased prevalence of known diabetes in recent years is due to increased ascertainment rather than an overall increase in diabetes prevalence.

A total prevalence of diabetes of approximately 9% suggests that many elderly diabetic subjects are not diagnosed in some areas of the UK. The importance of finding elderly diabetic subjects is outlined in Chapter 4. With increasing awareness of diabetes in the elderly, and with increasing routine blood glucose estimations, the proportion of elderly people with diabetes diagnosed would be expected to increase; this however will need an allocation or re-organisation of

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The prevalence of diabetes.

resources if they are going to be cared for properly, particularly since the number of elderly Britons at risk of diabetes is increasing.

## Diabetes in the elderly.

### Chapter 3: recruitment to the diabetic survey.

#### 3.1: introduction.

Non-recruitment causes two problems. Firstly the smaller sample size would increase the imprecision and widen the confidence intervals of the prevalence obtained purely by random variation within the sample. Secondly and more worrying, however, is the effect of systematic variation with the possibility that the subjects who were not examined had a significantly different disease prevalence to those examined; this would bias the results obtained in one direction rather than merely widening the confidence limits.

Of the 809 subjects not known to be diabetic, 583 had a glucose tolerance test (GTT) giving a recruitment rate of 72%; since 52 were known to be diabetic and did not need a GTT, the overall rate of ascertainment of glucose tolerance status was 74%; these rates are better than in the other two British surveys, Islington and Coventry, and the American NHANES II survey, but worse than most Finnish and Scandinavian surveys (see Figure 2.3). The relatively high recruitment rate is probably because the study was performed in one locality, specific to one problem and short [20]. The extremely high recruitment rate in some Fenno-Scandinavian surveys could be because the subjects had participated in previous surveys [26,27] and were thus the type of subject who would volunteer for a study; nonetheless, recruitment rates on previously untouched Fenno-Scandinavians are generally remarkably high [24,25,27]. The recruitment rate is sometimes difficult to ascertain from the report of the study; NHANES II [20] selected 8686 for a GTT, 7688 were interviewed, 5901 were examined, and 3872 had valid GTTs giving a recruitment rate of 44.6% to GTT; these figures obscure the fact that only 400 elderly subjects had a GTT in the NHANES II survey.

Whilst the 72% recruitment rate to the Melton survey appears laudable, any systematic bias could markedly affect the prevalence of diabetes obtained. Consequently I need to consider the effectiveness of recruitment to the diabetes survey, any known differences between those tested and those not tested and

### Recruitment bias in the diabetic survey.

whether these are likely to affect the prevalence obtained, and to review the findings of other investigators.

#### 3.2: accuracy of population age/sex register.

Subjects may avoid being tested by inaccuracies of the age/sex register being used. As discussed in Chapter 2, the Melton general practice age/sex register is thought to be accurate, because of the input from the Leicester University department of community health. Of the initial list of 924 subjects of all ages, 63 were not resident in the survey area at the time which the list of subjects was drawn from the population register of the local general practice; in the oldest, 85 year old group, 8 of the possible 70 subjects were not resident. Exact details are given in Figure 3.1 of the accuracy of the age/sex register used in Melton. This is a far more accurate register of subjects than the family practitioner list of City and Hackney which was inflated by 144% as discussed in Section 2.1 [54,55]. Patient registers would also be more accurate in Melton since the migration rate in Leicestershire is lower than many other parts of the country at 0.75% in and 0.70% out per year for subjects aged 60 and over [120].

Figure 3.1: table showing existence of Melton subjects (numbers of subjects).

Age/sex	Resident on 21/8/87	Not resident in area on 21/8/87:			Total
		Died before Aug 1987	Moved before Aug 1987	No trace ? why	
65: male	124	2 (2)	3 (1)	2 (1)	7
65: female	158	4 (2)	4 (0)	4 (0)	12
70: male	93	3 (3)	5 (2)	1 (0)	9
70: female	108	0 (0)	1 (0)	1 (0)	2
75: male	78	1 (0)	3 (0)	1 (0)	5
75: female	127	3 (1)	7 (0)	1 (0)	11
80: male	49	3 (3)	2 (1)	0 (0)	5
80: female	62	2 (1)	2 (1)	0 (0)	4
85: male	16	2 (1)	1 (0)	0 (0)	3
85: female	46	3 (2)	1 (0)	1 (0)	5
Total	861	23 (14)	29 (5)	11 (1)	63

\* number in parentheses are subjects included in number who had disappeared in only previous 8 months.

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A small proportion of elderly subjects are unregistered with their GPs [54], and would be missed from the Melton survey; however, it is generally felt that deflation of the practice list (failure to register patients) is not a problem [149], possibly due to the capitation system of payment of general practitioners. The organisation of the Melton general practice itself where the patients' registration details are checked at practice attendances, means that there are unlikely to be any errors of omission in the age/sex register used in the Melton survey.

Nonetheless some subjects were not at their registered address and information as to these subjects' fates was sought from the family practitioner committee list, electoral roll, neighbours, present occupiers of address, and residents with the same surname. Several subjects moved during the survey, and the two moving within Melton were approached. There were only 2 subjects with inaccurate addresses following change of address prior to the survey who were still registered with the Melton GPs, and both were approached. Apart from one man born 17/11/52, not 17/01/02, who is not included in any of the calculations, the subjects' dates of birth were correct. So the practice age/sex register contained predominantly real, live elderly people at the address given.

There was one person with known diabetes among the 29 who moved before 21/8/87, but this rate of known diabetes in those moving is not significantly different to the rate of known diabetes in the Melton survey of 6.0%; there seems to be no *a priori* reason why diabetes should be more or less common in people moving house.

Given the finding that diabetes increases mortality (see Chapter 6), one might wonder if the 29 who died before the survey, or the 11 with no trace might have caused an underestimate of the prevalence of diabetes. Firstly, however, any numerical effect would be small, and secondly this is a point prevalence study on subjects in Melton alive on 21/8/87. Thus although the effect of previous deaths on the present population and its prevalence of diabetes is interesting, it is not particularly relevant to the present study.

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Recruitment bias in the diabetic survey.

### **3.3: effect of area and recruitment letter.**

The next area where recruitment bias could occur would be during the actual performance of the study. The recruitment letter had both my heading and the local General Practice heading in an attempt to improve participation; unfortunately it would have been too difficult to have each patient's GP sign the letter. The recruitment letter was altered twice from the original (see Appendix 1). The initial letter was very scientific explaining the academic merit of the study; this was undoubtedly too complicated, and at the time the recruitment rate seemed poor. The second version was completely different, the main gist being that one could have diabetes without knowing it, and that this would cause gangrene of the legs. The second letter appeared to have a higher recruitment rate, but it was considered a little worrying for the subject; the third letter stated that one could have diabetes without knowing it, and that we could test simply for it. The first, second, and third recruitment letters were used in Asfordby, other villages, and then the town of Melton respectively; details are given in Figure 3.2. Despite personal feelings about the recruitment in different areas, the recruitment rates in the three areas with three different recruitment letters were similar and overall, and for each age group, area of testing had no effect on recruitment rate ( $\chi^2=3.34$ ,  $DF=8$ ,  $P>0.9$ ).

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Figure 3.2: table showing recruitment rate to diabetic survey by area (% and (numbers recruited/number approached)).

Age (Years)	Asfordby	Other Villages	Melton Mowbray
65	78 (14/18)	89 (31/35)	82 (174/211)
70	50 (7/14)	83 (20/24)	74 (107/144)
75	79 (11/14)	50 (9/18)	75 (112/148)
80	33 (2/3)	64 (9/14)	73 (55/75)
85	50 (1/2)	50 (3/6)	62 (28/45)
All ages	69 (35/51)	73 (72/99)	76 (476/623)

#### 3.4: effect of General Practitioner on recruitment.

It was also felt from talking to the subjects, that some general practitioners were very positive about the survey (TS, DL, PJ), and some were not (GM, BW).

However, when the recruitment by GP and age is examined (Figure 3.3) there is no significant effect ( $\chi^2=16.67$ ,  $DF=44$ ,  $P>0.995$ ) of the subject's GP. The subject's age has to be considered here since some GPs had a cluster of patients at one age. There is a lower than average recruitment rate for 2 cells in Figure 3.3 with a P value between 0.05 (ie 1 in 20) and 0.01 compared to all other cells; however, since there are 60 cells for each GP and age group, this could easily arise purely by chance with so many  $\chi^2$  tests. The Bonferroni method entails multiplying the significance value obtained (P) by the number of tests applied (k), and using  $kP$  as the P value [149a]; thus these two cells with low recruitment rate are not significant.

Recruitment bias in the diabetic survey.

Figure 3.3: table of recruitment by general practitioner, and age (percentage, and (numbers recruited/number approached)).

GP	Subject age (years):					
	65	70	75	80	85	All
DB	100 (13/13)	80 (4/5)	86 (6/7)	100 (5/5)	0 (0/1)	90 (28/31)
DC	81 (13/16)	64 (9/14)	62 (8/13)	67 (4/6)	0 (0/2)	67 (34/51)
MH	75 (30/40)	62 (13/21)	77 (17/22)	79 (11/14)	78 (6/9)	73 (77/106)
HH	80 (24/30)	70 (16/23)	81 (17/21)	73 (11/15)	75 (3/4)	76 (71/93)
PH	78 (14/18)	76 (16/21)	64 (9/14)	63 (5/8)	50 (2/4)	71 (46/65)
BK	60 (12/20)	76 (13/17)	92 (11/12)	100 (7/7)	83 (5/6)	77 (48/62)
DL	100 (23/23)	86 (12/14)	67 (8/12)	100 (2/2)	33 (2/6)	82 (47/57)
PJ	80 (20/25)	70 (14/20)	65 (13/20)	80 (4/5)	75 (6/8)	73 (57/78)
GM	67 (12/18)	78 (7/9)	57 (8/14)	71 (5/7)	67 (2/3)	67 (34/51)
TS	86 (19/22)	80 (8/10)	82 (18/22)	67 (4/6)	0 (0/1)	80 (49/61)
RT	95 (20/21)	92 (11/12)	57 (4/7)	50 (2/4)	0 (0/1)	82 (37/45)
BW	94 (17/18)	78 (10/13)	79 (11/14)	36 (4/11)	80 (4/5)	75 (46/61)



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#### 3.5: effect of fieldworker on recruitment.

Finally, there was no effect on recruitment of fieldworker approaching the patient (Figure 3.4)( $\chi^2=2.25$ ,  $DF=4$ ,  $P>0.1$ ).

Figure 3.4: table of recruitment by fieldworker (percentage, and (numbers recruited/number approached)).

Age (years)	Fieldworker		Refusal by letter
	SC	MB	
65	84 (151/180)	83 (67/81)	3
70	82 (53/65)	73 (79/108)	5
75	76 (16/21)	75 (115/154)	5
80	78 (18/23)	71 (48/68)	1
85	82 (14/17)	51 (18/35)	1
All ages	82 (252/307)	73 (327/446)	15

#### 3.6: effect of age and sex on recruitment.

Nonetheless, some patients were not tested due to death or migration during the study, and some were not tested due to refusal; figures are given in Figure 3.5.

Inspection of Figure 3.5 shows that the subjects' sex had no effect on recruitment rate.

### Recruitment bias in the diabetic survey.

Figure 3.5: table showing the diabetic survey recruitment and subsequent death (number of subjects).

Age / Sex	Known DM	Tested (*)	Refused (*)	Died during	Moved during	recr rate
65:ma le	3	100 (9)	18 (4)	2	1	83
:fema le	6	119 (10)	30 (2)	1	2	78
70:ma le	7	62 (6)	23 (2)	1	0	72
:fema le	10	72 (3)	24 (2)	2	0	74
75:ma le	8	50 (7)	16 (2)	3	2	70
:fema le	9	82 (6)	33 (5)	2	0	70
80:ma le	4	31 (10)	9 (3)	5	0	69
:fema le	2	35 (8)	17 (6)	7	1	58
85:ma le	2	7 (3)	4 (4)	3	0	50
:fema le	1	25 (10)	17 (6)	3	0	56
all:ma le	24	250 (35)	70 (15)	14	3	74
All:fema le	28	333 (37)	121 (21)	15	3	71
Total	52	583 (72)	191 (36)	29	6	72

Note: (\*)=subsequent deaths over next 54 months.  
recr rate=recruitment rate (Tested/tested+not tested) as %.

Acceptance rates in Melton fell with age from 80% in 65 year olds to 54% in 85 year olds with a simple correlation coefficient of -0.99 (t test for difference from zero correlation =-10.73, DF=3, 2 tailed P=0.0017). If the old have a much higher rate of diabetes than the elderly, this would artificially reduce the overall prevalence in our study. Although the East and West Finland study [26] has methodological problems, it had the same problems throughout and found that the prevalence was similar from 65 to 84. In Glostrup, Denmark, the rate was similar at 70 and 80 years of age [23]; one survey found a prevalence of 17% in over 85 year old Finns [24], and another study found a prevalence of 17.8% in Finns aged 65 to 74 [25]. In the Pima Indians the the prevalence was similar from 55 to 84 [150]. As already calculated in Section 2.19, the prevalence in Melton did rise slightly with age, but the age specific rates were all within each others 95% confidence intervals and there was no evidence of a decline in glucose tolerance from 65 to 85 years of age in the Melton sample. Although there might be a type 2 error in my analysis of diabetes prevalence changes with age, since the effect does not show in my figures, I presume that any effect on non-recruitment with

### Diabetes in the elderly.

age would be small. Thus I believe that the lower recruitment rate in the old had little significant effect on the calculated prevalence of diabetes obtained.

#### 3.7: relationship between subsequent mortality and recruitment.

All the subjects in the Melton survey were registered with the Office of Population Censuses and Surveys to identify subsequent deaths, whether or not they consented to participate; deaths are shown in Figures 3.5 and 3.6.

Figure 3.6: table of numbers of deaths observed and expected for each age/sex group and by acceptance/refusal of MOGTT (numbers of subjects).

Age/Sex	Deaths among tested: observed      expected		Deaths among refusers: observed      expected	
65:ma le	9	11.0	4	2.0
:fema le	10	9.6	2	2.4
70:ma le	6	5.8	2	2.2
:fema le	3	3.8	2	1.2
75:ma le	7	6.8	2	2.2
:fema le	6	7.8	5	3.2
80:ma le	10	10.1	3	2.9
:fema le	8	9.4	6	4.6
85:ma le	3	4.5	4	2.5
:fema le	10	9.5	6	6.5

There was no difference in death rate over the following 54 months between those that did and those that did not participate ( $\text{Chi}^2=6.73$ ,  $\text{DF}=9$ ,  $P>0.5$ ). Mortality will be considered further in Chapter 6 which shows that diabetes in the elderly is undoubtedly associated with an increased mortality. Thus it is important that the death rates are similar in those that accepted and those that refused the GTT, which is the case.

#### 3.8 the effect of social and cognitive factors on recruitment.

Residents aged 75 and over also participated in a questionnaire survey administered by trained local people [151], and this gave further information on subjects aged 75 and over who did and did not participate; this study was

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#### Recruitment bias in the diabetic survey.

organised by the Leicester University department of community medicine, and I am grateful to Dr C. Jagger for providing me with the data from this study. This questionnaire survey sought details of the residents' physical and mental health, sociodemographic features, and utilisation of social and medical services. Mental status was assessed by the information sub-test of the Clifton Assessment Procedures for the Elderly (CAPE) [152], and the Folstein mini-mental state examination (MMSE) [153]; physical status was assessed by perceived health, which correlates with subsequent mortality [154,155]. If the subject was demented, the required information was taken from the carer.

A subgroup of the questionnaire study participants had venous plasma glucose and serum fructosamine measurements.

The diabetes survey was performed from December 1987 to August 1988, and the questionnaires were administered from January 1988 to June 1988.

Questionnaire information was available for 21 of the 26 known diabetic subjects aged 75 or more, 218 of the 230 subjects agreeing to a GTT, and 80 of the 106 subjects who refused to have a GTT; differences were due to death, moving from the area or refusal to answer the questionnaire (the distribution of subjects refusing to answer the questionnaire can be found in Figure 3.9).

The findings of the questionnaire study are summarised in Figure 3.7 and show that the two groups of subjects refusing, and accepting a MOGTT were very similar in terms of social and demographic variables.

Again, the recruitment rate to the questionnaire survey was high, probably because small community studies recruit better than national studies, because the residents of Melton had experienced several previous studies, and because the study was performed in the subject's home.

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Figure 3.7: sociodemographic variables of Melton subjects relating to acceptance or refusal of GTT.

Variable	Subjects tested (number)	Subjects not tested (number)
Male:Female	83:135	25: 55
Community:Institution Resident	213: 5	79: 1
Hospital OP last year Y:N	82:136	18: 62 *
Hospital IP last year Y:N	40:178	15: 65
Hospital A/E last year Y:N	26:192	11: 66
Any Hospital last year Y:N	104:114	29: 51 *
Seen GP last year Y:N	163: 49	54: 25
Dementia: non-dementia (CAPE<8)	4:214	8: 72 ****
Perceived health Good:Fair:Poor	118:83:12	45:29:5
Social Class 1:2:3M:3M:4:5 (Forces)	8:47:26:101:26:5 (5)	1:13:5:38:18:1 (3)

Note: OP=out-patient; IP=in-patient; A/E=accident & emergency dept. Y=yes; N=no; GP=general practitioner.

\* p<0.05 : \*\* p<0.01 : \*\*\* p<0.001 : \*\*\*\* p<0.0001

Some figures do not total 100% due to incomplete data.

There was no difference between the two groups regarding use of district nurse, health visitor, home help, meals on wheels, reported visual or hearing difficulties ( $P>0.1$ ). Although perceived health status and diabetes have not previously been examined together, the morbidity associated with diabetes [40,41] is well recognised; thus it is important to note that subjects accepting and subjects refusing the GTT had similar perceived health.

It is not surprising to learn that the San Antonio survey [156] found lower participation rates in lower socioeconomic areas, and that the 1973 NHIS survey [123] found inverse relationship between income and prevalence of known DM; thus non-recruitment in the USA might be associated with a higher prevalence of diabetes in those not tested. It is known that known diabetes was more common in lower social class areas of the UK [122]. It is thus fortunate that those refusing a MOGTT had a similar social (see Figure 3.8) class to those accepting the MOGTT ( $\chi^2=8.61$ ,  $DF=5$ ,  $P=0.13$ ).

### Recruitment bias in the diabetic survey.

Figure 3.8: table showing social class as percentage of subjects accepting and subjects refusing GTT (%).

Social Class	Tested (%)	Refused (%)
1	3.7	1.3
2	23.4	16.5
3	58.1	54.4
4	12.0	22.8
5	3.3	1.3
Forces	3.3	3.8

Other studies where subjects were interviewed prior to being offered a GTT have also found that social class did not affect recruitment to a later GTT [117,157].

There was however a significant tendency for the group tested to have received hospital outpatient treatment in the last year; there was no difference between the two groups in terms of in-patient treatment, accident and emergency department treatment or contact with local GPs. Other studies found more usage of medical services by non-respondents of North American surveys [157,158], while our study found the reverse, probably reflecting differences in both the study populations and the health care systems. Although subjects known to have diabetes have more outpatient attendances, inpatient admissions and greater hospital bed occupancy than the general public, a study from Fredericia [42] found that Danes in the year prior to the discovery of their fasting hyperglycaemia had shorter hospital bed occupancy than Danes without fasting hyperglycaemia. However, these are subjects with fasting hyperglycaemia which is not necessarily diabetes (see Sections 2.3, 4.3), the actual number of admissions and outpatient attendances are not given, and longer admissions may have had a greater chance of revealing diabetes and transferring the patient to the known diabetic group.

In the Leicester hospitals, many new patients have a random blood glucose measurement (on a clotted specimen if a fluoride oxalate specimen is unavailable); since the patient is presumably ill and under stress, it would seem likely that diabetic subjects in this group are found, and transferred to the known diabetic group of subjects, decreasing the prevalence of undiagnosed diabetes in this group.

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However, none of all the 52 known diabetic subjects were discovered at outpatients during 1987 (6 were discovered as inpatients in 1987, 6 were found by their GP in 1987, and the remaining known diabetic subjects were found over 1 year ago); thus this increased outpatient clinic usage by the tested group does not seem to introduce a significant bias.

The main difference between the tested and refused groups is in the presence of cognitive dysfunction as shown by a CAPE score lower than 8 (1.8% versus 10% respectively), which was far commoner in the refused group (2 tailed Fisher's exact  $P=0.0037$ ); the relationship between diabetes and cognitive dysfunction in the Melton diabetes survey is given in greater detail in Figure 3.9 which shows the MMSE results grouped into low (<22), middling (22-23), and high (>23) categories for each type of glucose tolerance status, following previous work using the MMSE in Melton [159].

Within each age group, there were no differences in sex distribution of MMSE result ( $\chi^2 P>0.1$ , and Fisher's exact  $P>0.1$  when reduced to 2 by 2 tables), and thus further analysis was performed with the sexes combined.

Figure 3.9: results of MMSE by result of GTT (numbers of subjects).

Subjects by GTT result	Male MMSE result				Female MMSE result			
	Ref	<22	22-23	>23	Ref	<22	22-23	>23
<b>75 years</b>								
Known DM	0	3	0	4	0	1	2	6
New DM	0	0	0	1	0	0	0	1
IGT	0	0	0	7	0	0	0	5
Normal	4	1	1	36	1	7	0	67
Refused GTT	2	0	1	13	4	4	2	23
<b>80 years</b>								
Known DM	2	1	0	1	1	0	1	0
New DM	0	0	0	3	0	0	0	1
IGT	1	0	0	4	0	0	0	0
Normal	0	1	1	21	2	7	3	22
Refused GTT	2	1	0	6	5	4	1	7
<b>85 years</b>								
Known DM	0	0	0	1	0	0	0	1
New DM	0	0	0	0	0	0	0	3
IGT	0	0	0	2	0	2	1	1
Normal	0	1	1	3	1	6	3	6
Refused GTT	0	1	0	3	3	6	1	7

Note: Ref=refused MMSE.

#### Recruitment bias in the diabetic survey.

Analysis of data contained within several contingency tables can be problematic [160], but each age group was reduced to various 2 by 2 contingency tables to give adequate cell sizes and to allow a Mantel Haenszel  $\chi^2$  test for a series of 2 by 2 tables to be applied [160a]: a MMSE cut-off at 23/24 was used since this has been found to give a reasonable sensitivity and specificity (over 80%) for detecting all grades of dementia in Melton [159], and has been found to be the optimum cut-off by other investigators [161]. It should be emphasised that a low score on these tests of cognitive function does not necessarily mean a diagnosis of dementia since there are other causes of cognitive impairment such as depression; hence the specificity of only 80%. Results of this analysis are given in Figure 3.10.

Figure 3.10: results of Mantel Haenszel test for low MMSE result in subjects with different glucose tolerance.

Glucose tolerance status of subjects compared	Chi <sup>2</sup>	Mantel P	Haenszel: Odds R.	95% CI	
Known DM/not known DM	6.72	0.015	3.38	1.35	- 8.48
Any DM/normal	0.72	0.395	1.54	0.57	- 4.13
Known DM/normal	6.17	0.013	3.30	1.29	- 8.48
Found DM/normal	5.87	0.015	5E-14	9E-25	- 0.003
Accepted GTT/refused GTT	1.67	0.196	0.70	0.41	- 1.20

Note DM=diabetes; GTT=glucose tolerance test.

The important result is that those accepting and those refusing a GTT had similar MMSE ( $P=0.195$ ) when allowance is made for age by the Mantel Haenszel test; thus the increased numbers of subjects with cognitive impairment in the group refusing a GTT relate to the refusing group having a larger proportion of older people who have lower cognitive function (Figure 3.11).



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Figure 3.11: proportion of sample subjects with MMSE below 24 and proportion refusing a MOGTT for each age group.

Age (years)	Proportion low MMSE (%(95% CI))	Proportion refusing GTT (%(95% CI))
75	11.9 ( 7.6-17.5)	27.2 (20.9-34.3)
80	23.5 (15.0-34.0)	28.3 (19.4-38.6)
85	44.9 (30.7-59.8)	41.2 (27.6-55.8)

Did they refuse because they had cognitive impairment, and just happen to be older, or did they refuse for some other reason associated with age and just happen to be demented? It is thus still interesting to know whether diabetes is associated with cognitive impairment in the Melton survey.

Studies have shown that elderly diabetic subjects do have impaired cognitive function [162-166], but these mild deficits were of dubious relevance to daily living, the studies excluded subjects with dementia [163-166], and generally used a large battery of tests to show the deficit [162,164-166]. Interestingly, worse cognitive function in these tests was associated with worse glycaemic control [162-166].

Dornan's study [40] examined 98 known diabetic subjects and found that 15 had a Hodkinson mini-mental test less than 10 [40, personal communication], compared to only 1 of 98 age/sex matched subjects not known to be diabetic; this is a significant difference (2 tailed Fisher's exact  $P=0.0003$ ), but most people would use a cut-off of below 8 rather than below 10 [167].

However, other workers have either found no decreased cognitive function in elderly diabetic subjects [168], or found that the decreased cognitive function in diabetic subjects is totally explained by depression in the diabetic subjects [169]. Other workers have found that diabetes is associated with depression [115].

Studies looking at dementia sufferers found a low prevalence of known diabetes in Alzheimer type dementia (SDAT), from 0 to 6%, but a higher incidence in multi-infarct dementia sufferers (MID), from 12 to 30% [170-173]. These studies vary in subject nationality, sample size, whether or not mixed MID/SDAT subjects were included as MID subjects, the diagnostic methods to classify the

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#### Recruitment bias in the diabetic survey.

dementias, and the care in accepting the diagnosis of diabetes, which may be erroneous [133]. These studies all show a raised prevalence of diabetes in MID, and a decreased prevalence in SDAT. Studies of the type of dementia in populations suggest that 50-65% is SDAT, 12-24% is mixed SDAT/MID, and 8-29% is MID [171,174].

Thus studies looking at subjects with dementia often do not fully know the subjects glucose tolerance status, and diabetic detection and complication surveys rarely examine cognitive function. It may be that diabetic subjects are less likely to develop SDAT, but more likely to develop MID.

The data from the Melton surveys (Figure 3.10) suggest that in comparison to subjects with normal glucose tolerance, subjects with known diabetes are more likely to have a low MMSE result (odds ratio 3.3, 95% CI 1.29-8.48), and subjects with newly diagnosed diabetes are less likely to have a low MMSE (upper 95% CL of odds ratio 0.003) compared to normal glucose tolerance subjects; overall, these effects cancel out so that all diabetic subjects combined had similar cognitive function to normal glucose tolerance subjects.

In subjects agreeing to a GTT, a diabetic result was associated with less chance of a low MMSE result. The subjects who refused a GTT were more likely to be older and to have cognitive impairment, and one wonders whether they were less likely to have undiagnosed diabetes. This bias would seem biologically implausible, since it is unlikely that diabetes would be neuroprotective, but it is thought that subjects with Alzheimer's disease are less prone to diabetes [170-172].

Perhaps I am making a type 2 error with the small numbers involved, but the 95% confidence limits are well below 1.0.

I feel that the problem with cognitive impairment and GTT refusal are unlikely to significantly alter the prevalence of diabetes obtained because within each age group and over all age groups (Figure 3.10), cognitive impairment was not associated with refusal. Also, considering the whole study group, the subjects with cognitive impairment constituted only a small proportion of the sample.

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However, the relationship between diabetes, cognitive function and participation in surveys would bear further study.

The most significant association from the above data (Figure 3.9) was that subjects refusing a GTT were more likely to refuse the MMSE (Mantel Haenszel  $\chi^2=11.34$ ,  $P=0.0008$ ; odds ratio 4.07 (95% CI 1.8-9.2)).

### 3.9: available information from other tests for diabetes in Melton.

A random sub-group of the questionnaire study participants had glucose and fructosamine levels measured by the Leicester University department of community health; approximately 50% of those approached consented to venepuncture, and the results are expressed in Figure 3.12.

Figure 3.12 Glucose and fructosamine values in sub-group of questionnaire subjects.

	MOGTT tested	MOGTT refused
Glucose mean (1SD) (mmol/l)	5.48 (1.63)	5.99 (1.93)
Number	27	10
Fructosamine mean (1SD) (mmol/l)	1.69 (0.163)	1.72 (0.168)
Number	26	9

Examining the results from the questionnaire study subgroup subjects' glucose and fructosamine measurements, there was no difference between subjects that accepted or refused a GTT (t tests and Wilcoxon rank sum tests,  $P>0.1$ ).

Although the value of fructosamine in diagnosing diabetes in this population and survey is documented as excellent in Chapter 4, the actual number of subjects is too small to draw firm conclusions, and with only a 50% acceptance rate for venepuncture, there may well be some study bias. All that one can say for certain is that there were no gross differences between the two groups.

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Recruitment bias in the diabetic survey.

**3.10: review of other studies.**

There are undoubtedly many other potential confounding features which I have not considered due to lack of data, such as family history, body weight, medication etc. The NHANES II survey [20,157] interviewed subjects aged 20 to 74 years at home prior to a GTT at a later date and found that amongst the subjects interviewed, there was no bias towards further participation due to age, sex, income, physician's diagnosis of diabetes, body weight, level of exercise, recent hospital admissions, taking of medication, heart attack, heart failure, "hardening of arteries", stroke, high blood pressure, cataracts or glaucoma. However, it was found that those with a family history of diabetes were more likely to participate in a GTT and have undiagnosed diabetes than those without. Those with a family history of diabetes comprised 16% of those interviewed at the start of the survey, but comprised 18.3% of those undergoing a GTT; yet prevalences of new diabetes were 4.8% and 2.9% when there was or was not a positive family history, respectively; the overall effect of this was small, and the overestimate probably increased prevalence of new diabetes from 3.187% to 3.231% [20]. It was also noted that both a positive family history and obesity were each associated with a doubling of the risk of diabetes but that the obese diabetics were previously undiagnosed while the diabetic subjects with a positive family history of diabetes were generally known. Thus many high risk subjects with a family history of diabetes may be identified prior to a screening survey; this could be due to astute physicians testing the subjects with a family history of diabetes, or the families themselves having the knowledge and equipment to test themselves. However, NHANES II had an 88% recruitment rate to the interview which might bias the results; those not agreeing to be interviewed were similar to those interviewed regarding age, sex and race but there are no other data on the refusing subjects. The 1976 NHIS had an amazingly high 96% acceptance rate to interview, although no examination was done [123]; it is thought that the total prevalence of diabetes was the same in both surveys since both had prevalences of known diabetes of 3.0 to 3.4% and the number of unknown diabetic subjects is generally

### Diabetes in the elderly.

approximately equal to the number of known diabetic subjects [20]. Comparison of the NHIS subjects to the subjects examined in NHANES II reveals similar perceived health status, hospital stays, known heart disease, known diabetes, family history of diabetes, and body mass index [157]. So it appears that non-recruitment was not a significant problem in the NHANES II study for diabetes prevalence.

The Israeli hypertension and glucose intolerance survey also interviewed prior to GTT at a later date [117]; those agreeing to be interviewed had similar age, sex and race to those refusing interview. Those proceeding to GTT again did not differ in terms of age, sex or race and were also similar to those interviewed in terms of body mass index, blood pressure and medication use.

However, all these studies are using surrogates to determine whether refusing subjects had differing glucose tolerance status and did not actually know the glucose tolerance status of those that refused a GTT. Agner et al [23] in Glostrup recruited 73% of Danes aged 80 to a GTT who had had a GTT ten years earlier; those accepting had the same glucose tolerance 10 years earlier as those refusing a GTT; unfortunately this is a group of subjects who had already agreed to the GTT at age 70, and were thus preselected as the type of subject who would agree to be tested. However, unless one can force subjects to have a GTT, the Glostrup study provides the best evidence available regarding the glucose tolerance status of subjects refusing a GTT.

### 3.11: conclusions.

Previous studies have found that non-recruitment is generally not a problem in terms of prevalence bias. In Melton, factors which might bias the results, such as social class, perceived health status, hospital admissions, and future mortality, were similar in those that accepted and those that refused a MOGTT. Age was associated with a decline in recruitment rate but the prevalence of diabetes does not appear to increase significantly over the age range studied.

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#### Recruitment bias in the diabetic survey.

Scores of cognitive function were lower in subjects refusing the MOGTT, but, allowing for the effect of the lower recruitment rate with increasing age, cognitive function did not alter participation in the survey. The group most prone to have cognitive dysfunction and to refuse the MOGTT were the 85 year olds who constituted a small part of the population studied.

Finally, from a mathematical point of view, the high recruitment rate of the Melton survey, and the high prevalence of known diabetes means that the prevalence of diabetes in those not tested would have to be grossly different from the prevalence in those tested to have much effect on the overall prevalence. The survey found 52 known diabetic subjects, tested 583 subjects finding 19 new diabetic subjects, and 226 were not tested; if the prevalence of diabetes is the same in those tested and not tested, then the prevalence is 9.11%; however, if the prevalence in those not tested is half or double the prevalence in those tested, then the prevalence changes to 8.63% or 9.97% respectively.

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### Chapter 4: screening for diabetes.

#### 4.1: why screen for diabetes?

Diabetes is defined biochemically by the blood glucose concentration, often in response to a glucose load [50,51]. Type 2 diabetes may be asymptomatic in the elderly, but it has long been realised that screening for diabetes is worthwhile as Spence wrote in 1920, "Since this is a condition that can be easily corrected by a slight modification of diet, its early recognition by means of a blood sugar estimation would be of value" [64]. Deaths from diabetic ketoacidosis occur predominantly in elderly subjects not previously known to be diabetic [45]. Delay in diagnosis of diabetes is associated with the development of complications [175], although I fully accept that association does not mean causation. Footcare [38,39] and eyecare [30,33,34] can only prevent morbidity if the diabetic subject is identified. In the elderly diabetic, it has been shown that retinopathy [176,177] and cognitive impairment [162-164,166] are associated with a poorer degree of diabetic control and that improving control may improve cognitive function [178]. In a sample of 987 diabetic subjects with diabetes onset over age 30, high glycosylated haemoglobin levels were associated not only with degree of retinopathy at the time of initial examination, but also with the future development of retinopathy [179]. Renal function can also be improved in the type 2 diabetic subject by good glycaemic control [180]. Again, good glycaemic control is dependent upon recognising the diabetes.

Hayes *et al* [181] in Cardiff discharged 103 stable subjects with NIDDM, average age 60 years, to GP care and continued hospital care for 97 subjects; at 5 year follow up, the subjects under GP care had more deaths (18 versus 6 in hospital control subjects; Fisher's exact  $P=0.017$ ) and worse control (GP  $HbA_1$  10.4% versus hospital  $HbA_1$  9.5%;  $t=2.52$ ,  $P<0.02$ ). It is not possible to say whether the improved survival in the hospital group is due primarily to improved glycaemic control, or due to a better overall care package; whatever the reason, this study shows that good diabetic care is good for the patients.

#### Methods of diabetes screening.

Thus it is important for previously undiagnosed diabetic subjects to be identified, but what are the requirements for a successful diabetes screening program?

As well as the belief of the medical staff that it is worthwhile to screen for a condition, the population being screened have to hold similar views, although not necessarily for the same reasons, otherwise they will not participate; thus adequate publicity and education directed at the general public are necessary. It would be necessary to monitor recruitment so that any sectors of the population with poor participation can be identified and specially targeted. The population is also important from a further point of view; if a condition is common, it is more easy to find the condition than if it is uncommon.

In selecting the screening test, one obviously wishes a test that is sensitive and specific; it would be rare to have a test which is both highly sensitive and highly specific, and thus if there is a range of results, it is necessary to pick the correct cut-off value for defining a positive result; a receiver operating characteristic graph can be drawn (specificity plotted against sensitivity for different cut-off values) [195] and the optimum cut-off is found in the upper right hand corner of the graph. The test should also be safe and as least intrusive as possible. It would also need to be economical for mass use and this might suggest that the tests should be administered and interpreted by the population to reduce costs. Thus the test should be simple to perform and understand. In one evaluation of a screening method, only 59% of subjects actually used the free urine testing kits which they had had to collect from local drugstores, and only 23.5% of subjects with glycosuria followed the written instruction to seek medical help [181a]; in a different study, urine was collected in drugstores (the authors do not reveal how), urine was tested professionally, and subjects with glycosuria were sent a letter telling them to seek medical help, which 71% did [181b]. Thus the subjects probably require a large degree of supervision if they are to act correctly on the findings of simple tests such as urinalysis.

The personnel running the screening system must also be enthusiastic and well trained, since this is the face of the system that the population will actually meet.



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Finally, it is important that any subjects found to have diabetes rapidly receive high quality diabetic care; thus the screening program must consider the follow up of these subjects, and overall the whole program needs extremely good organisation.

At present the optimum test for defining a person as diabetic is the modified oral glucose tolerance test (MOGTT) [51], but even this requires the subject to take the complete glucose load whilst fasting, with a blood glucose estimation two hours later, and is thus time consuming to organise. Is there a simpler method for population screening?

#### 4.2: previous use of urinalysis for diabetes screening.

Urine analysis for glycosuria was the standard screening test for many surveys until the mid 1960's, but the elderly diabetic with a high renal threshold may not show glycosuria. For instance, the Bedford survey [66] found 90 diabetic subjects in 570 people with no glycosuria and a similar exercise in Birmingham [70] produced 66 new diabetic subjects in 345 subjects without glycosuria. On the other hand, 678 of 939 subjects with glycosuria in Bedford and 338 of 465 subjects with glycosuria in Birmingham [58] were not diabetic. However, these surveys were performed prior to the introduction of the concept of impaired glucose tolerance (IGT); examining data from the second Birmingham survey [70], shows that of subjects aged 50 and over who did not have glycosuria, only 6 of the 48 subjects then thought to be diabetic in 1962/3 would be considered diabetic today and reviewing the diagnosis of subjects in the Rochester community diabetes surveillance scheme revealed that 16.5% of the diabetic subjects actually had IGT [59]. In an article anticipating the introduction of IGT by many years [140], Butterfield and Keen reviewed data from the Bedford survey with an 11.1 mmol/l cut off for diabetes and calculated that postprandial urinalysis would miss half the undiagnosed diabetic subjects; they also noted that the renal threshold for glycosuria rose with age and with the female sex. The use of urinalysis in the Islington community survey was recently reported [182] in which

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only 8 of the 25 new diabetic subjects had glycosuria on fasting urine specimens; the sensitivity was increased to 73% by using 2 h post glucose load urine samples, at the expense of specificity. Thus urinalysis fails to identify many diabetic subjects.

#### 4.3: previous use of fasting plasma glucose level for screening.

Some people still favour the fasting plasma glucose (FPG) for diabetes testing [183], "since the FPG varies least with age". However, this suggests that it is a poor test since it misses the age related increase in diabetes prevalence. For instance, the NHANES II survey [20] found no significant increase in FPG with age but the 2 h post glucose load blood glucose increased significantly with age. It is a basic medical principle that if hypofunction of a system is suspected, you stress it [184], and it is a basic principle of aging research that a stress test is more sensitive at detecting age related reduction in functional reserve than a test at rest [185]; an overnight fast is not a stress.

These theoretical considerations are reinforced by Simon *et al's* study of subjects referred for diabetes testing [186] which showed a sensitivity of the FPG of 52%, ie the FPG misses half the diabetic subjects. Modan [117] also found the FPG to be of little use in a population survey with 49 of 134 new diabetic subjects having a FPG below 6.4 mmol/l. The Rancho Bernardo study of fit American retirees aged 60 and over revealed that only 69 of 254 newly diagnosed diabetic subjects had a raised FPG [21].

Epidemiologists still favour the FPG since it does correlate well with the prevalence of diabetes in populations; however, this is because the number of false negatives from the test are matched by the number of false positives [187]. This is useful in comparing different populations for diabetes prevalence, but is less useful for examining one population closely. Importantly, the diabetic subjects missed by the FPG are just as likely as subjects with a raised FPG to develop specific diabetic symptoms [85,86] as mentioned in Section 2.3. The studies supporting the use of the FPG [187] used a lower cut off than that recommended

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by the WHO and also used non-white Pacific populations. With the NHANES II survey [20] finding that the FPG missed the age related increase in prevalence of diabetes, I believe that one has to treat any prevalences derived from the FPG with extreme caution; now the WHO omit the FPG from diabetes screening requirements [51].

Finally, the FPG is influenced by the season; in studies ranging from California [188] to 30 feet underground in the Antarctic [189], levels were lowest in the spring and highest in the winter, despite allowance for different weight and physical activity of the subjects. However, the seasonal variation post glucose load or post prandial is proportionally less, and the number of subjects exceeding a 95<sup>th</sup> percentile or 11.1 mmol/l cut-off does not alter with the season [190].

Thus for several reasons, I feel that the FPG is very unsuitable as a screening test.

#### 4.4: the use of the random plasma glucose level for screening.

The use of the random blood glucose (RBG) was investigated in 1957 when food handlers had a pre-employment random blood sugar measured [113]; 152 subjects with random whole blood glucose levels below 7.2 mmol/l were subjected to a formal glucose tolerance test (GTT) and 12 were found to be diabetic (2 h whole blood glucose > 10.0 mmol/l); these 12 diabetic subjects had fasting blood sugar levels from 3.6 mmol/l to 5.5 mmol/l, but the important point is that 8% of these subjects with RBG levels below 7.2 mmol/l had a diabetic GTT result. A study of pregnant women [78] also found a very poor sensitivity for detecting diabetes using the random plasma glucose (RPG), although the sensitivity increased in mid-afternoon reflecting the diurnal variation in glucose tolerance: the effect of diurnal variation on glucose tolerance [96,97] should be taken into account during diabetes screening, but it is sometimes neglected [26]. The Coventry diabetes survey [76] prescreened with a random capillary whole blood glucose level, and subjects with blood glucose > 6.0 mmol/l within two hours of a meal, or with blood glucose > 4.4 mmol/l more than two hours after a meal were subjected to a GTT; 130 subjects who did not 'qualify' for a GTT were tested with a GTT, and 2

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subjects, both over 70 years old, were found to be diabetic [77]. Of 442 subjects who 'qualified' for a GTT, 64 were found to be diabetic.

The use of the random plasma glucose in elderly subjects admitted to a geriatric department was examined in 1972 when all subjects with  $\text{RPG} > 10.0 \text{ mmol/l}$  were diabetic, but unfortunately the investigators did not examine subjects with lower RPG levels to see how many of these had unrecognised diabetes [191].

Thus the application of meal related criteria to the random glucose level does identify a group highly likely to have diabetes, but still misses a small number of diabetic subjects, who may well be elderly.

#### 4.5: the use of glycosylated products for diabetes screening.

Recently, the measurement of glycosylated haemoglobin and fructosamine, glycosylated plasma proteins, have become available which reflect the average plasma glucose level over a period of time. The use of one of these tests to replace the MOGTT would be attractive.

Several studies have looked at the use of glycosylated haemoglobin in diagnosing diabetes; these studies vary regarding study population, recruitment bias, technique for measuring glycosylated haemoglobin, and method of diagnosing diabetes. Modan *et al* examined a stratified sample of Israeli citizens using a GTT and measuring total glycosylated haemoglobin; they found that a glycosylated haemoglobin cut-off value of 8.5% found only 18 (26%) of the 68 new found diabetic subjects [117], but reducing the cut off level to 6.0% increased the sensitivity to 92% at the expense of specificity. A Pima Indian population study used the more precise  $\text{HbA}_{1c}$  measurement and attained a sensitivity of 85%, but this still missed 19 of the 131 new diabetic subjects [192]. In the Islington survey, a total glycosylated haemoglobin cut-off value of 8.1% gave a sensitivity of 90% and specificity of 46% [193] for diabetes. The previous surveys using  $\text{HbA}_1$  for screening are summarised in Figure 4.1.

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Figure 4.1: table of results using glycosylated haemoglobin for screening.

Study	HbA <sub>1</sub> or HbA <sub>1c</sub>	Cut-off (%)	Sensitivity (%)	Specificity (%)	General Population
Islington [193]	HbA <sub>1</sub>	8.1	90	46	Almost
Whampton [194]	HbA <sub>1</sub>	7.8	100	100	No
Pima [192]	HbA <sub>1c</sub>	6.03	85	91	Almost
Israel [117]	HbA <sub>1</sub>	6.0	92	21	Yes
Netherland [28]	HbA <sub>1</sub>	8.6	67	97	No
Tokushima [197]	HbA <sub>1c</sub>	5.7	92	96	Almost
Cardiff [200]	HbA <sub>1</sub>	8.0	36	90	No
INSERM G [196]	HbA <sub>1</sub>	7.8	15	100	No
INSERM S [186]	HbA <sub>1c</sub>	6.0	60	91	No

It should be noted that many of the studies examined only subjects referred for diabetes testing [194,186,196], some studies examined a population, but oversampled the subjects likely to have diabetes without allowing for this in calculating the performance of the test [192,193], and only a handful are truly population based [117]. These centres studying highly preselected groups of subjects likely to be diabetic makes it easy for the new test to find the subject sought and perform well [198]. Although HbA<sub>1c</sub> is increased by hyperglycaemia, the other fast haemoglobins, HbA<sub>1a</sub>, HbA<sub>1b</sub>, can be raised for other reasons, such as alcohol abuse [199], thus confusing the picture if one used the total HbA<sub>1</sub> and explaining some of the differences between the different studies.

More recently, the use of HbA<sub>1</sub> in the elderly has been studied and found to be very poor at finding diabetic subjects [200]; however, this study has been severely criticised for various reasons such as use of total glycosylated haemoglobin, definition of diabetes and the recruitment of subjects from a geriatric clinic [201]. Thus the glycosylated haemoglobin would appear to be of limited value.

The first study using fructosamine in diabetes screening was based on 83 hospital visitors with normal random blood sugar as the non-diabetic control group [202]

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and examined those subjects referred for a GTT. A Dutch group performed a similarly poor study [195] in terms of definition of normal range, and preselection bias of the group to be tested for diabetes. In fact, most studies investigating the use of fructosamine for screening have been marred by poor subject selection for the non-diabetic control group, and/or have not been based on the general population [195,196,202-204].

Two studies used fructosamine in population based screening surveys employing GTTs [28,205]; one achieved results in elderly Dutch with predictive values of 65% positive test and 85% negative test [28], although patient recruitment details are omitted. However, on examining Tanzanians of all ages, predictive values of 44% positive test and 97% negative test [205] were found. One other study was population based on Kawerau, but omitted to screen for undiagnosed diabetic subjects [206]!

On comparing the fructosamine to the glycosylated haemoglobin, the fructosamine performed marginally better than the glycosylated haemoglobin in one study (sensitivities 52% and 44% respectively) [195], but another study found the glycosylated haemoglobin superior [196].

Since fructosamine is cheap and relatively simple to measure and because I believe that it is worthwhile to screen for diabetes, the use of fructosamine for screening was investigated whilst screening the elderly of Melton Mowbray for diabetes.

#### **4.6: the use of fructosamine to screen for diabetes in Melton: subjects and methods.**

All subjects aged 65 years or more who were tested in the diabetes survey were included in this study, ie both the main sample and the spouses/neighbours; this was to increase the number of diabetic subjects for analysis.

During the MOGTT a clotted blood sample was taken at 2 hours for serum albumin and fructosamine measurements, at the same time as the fluoride oxalate

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specimen for glucose estimation. The blood samples were kept at 4° C, separated within 4 hours, and frozen for later analysis.

The method of diagnosis of diabetes was as in the main survey, ie with repeat testing if a 2-hour glucose concentration was 11.1 mmol/l or more [51].

A random sample of subjects with normal glucose tolerance was obtained by storing the serum samples in boxes of 100 by order of venesection, and taking 35 specimens after shaking the box.

The fructosamine level was measured on this random sample of subjects with normal glucose tolerance and on subjects with any abnormality of glucose tolerance.

Serum fructosamine was measured using the standard method of Johnson, Metcalfe and Baker [207] on a Cobas Bio centrifugal analyser (Roche Products Ltd, Welwyn Garden City, UK). The reagent was prepared in-house and comprised 0.1 mmol/l sodium carbonate buffer (pH 10.35 at 20°c) containing 0.25 mmol/l nitro blue tetrazolium. The calibration material was a glycated albumin pool, standardised against an aqueous solution of 1-deoxy-1-morpholinofructose which contained 40 g/l human albumin. The within batch coefficient of variation (CV) was 1.2% (mean 1.69 mmol/l) and between batch CV was 2.2% (mean 1.22 mmol/l).

Serum albumin was measured in these subjects using the bromocresol green method on a Technicon SMACII analyser (Technicon Instruments, Basingstoke, UK).

#### **4.7: results of the use of fructosamine for screening in Melton.**

742 residents were tested; 26 new diabetic subjects were found, 56 people had IGT, and 661 had normal glucose tolerance.

264 subjects with normal glucose tolerance were selected as control; further details of these subjects are given in Figure 4.2, but the important point is that they resembled the whole group of normal subjects in terms of age (2 tailed Mann-

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Whitney U test  $P=0.39$ ), sex (2 tailed Fisher's exact  $P=0.23$ ), and MOGTT result (2 tailed Mann-Whitney U test  $P=0.87$ ).

Figure 4.2: table showing details of all normal glucose tolerance subjects and subjects in normal fructosamine control group.

	Normal MOGTT subjects	Normal fructosamine control group
Number	661	264
Number male	284	121
Ages (years):		
Maximum	87	86
Upper quartile	75	75
Median	70	69
Lower quartile	65	65
Minimum	65	65
MOGTT result (mmol/l)		
Maximum	7.7	7.7
Upper quartile	5.6	5.5
Median	4.7	4.8
Lower quartile	4.0	4.0
Minimum	1.3	1.85

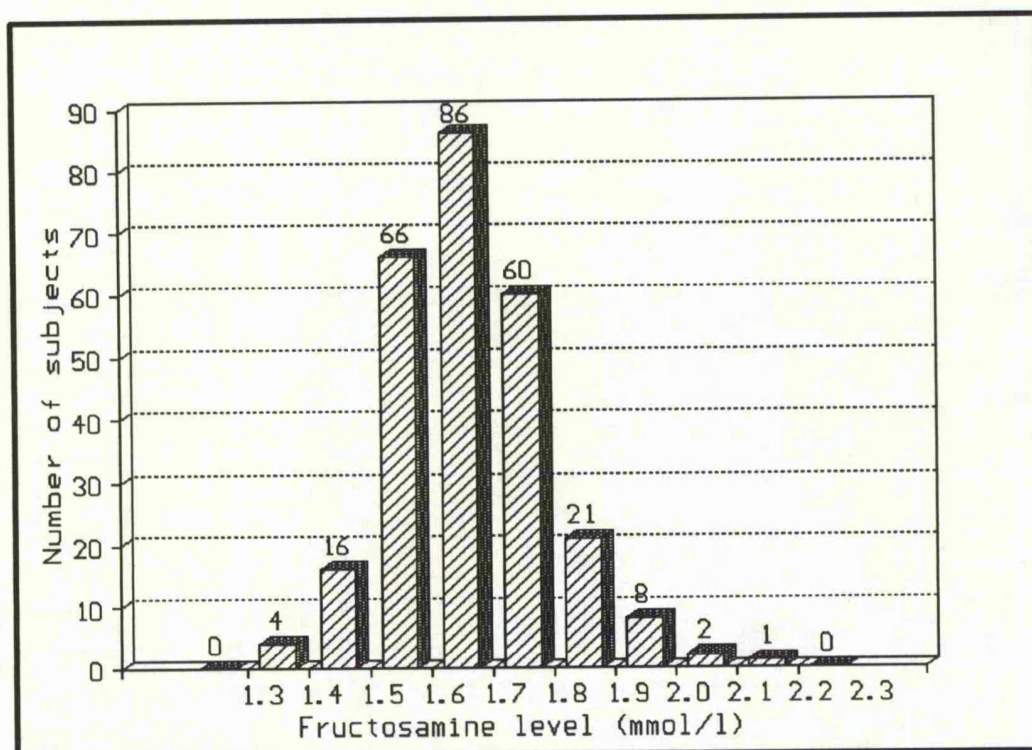
The serum fructosamine concentration in 264 subjects with normal glucose tolerance had a Gaussian distribution (distribution fitting to Gaussian distribution  $\chi^2=7.71$ ,  $DF=6$ ,  $P>0.1$ ; Shapiro-Wilk test  $W=0.98$ ,  $P=0.17$ ), with a mean of 1.67 mmol/l and standard deviation of 0.126 mmol/l (see Figure 4.3).

There was no sex difference in fructosamine level in normal subjects (female  $n=143$ ; mean=1.672 mmol/l,  $SD=0.0130$ ; male  $n=121$ ; mean=1.664 mmol/l,  $SD=0.122$ ;  $t$  test  $P>0.1$ ). Age did have an effect on fructosamine level (simple correlation coefficient=-0.185; deviation from nil correlation  $t=-3.05$ ,  $P=0.0025$  [208]); since fructosamine is predominantly glycated albumin [202] and these normal subjects' fructosamine levels do correlate with albumin levels (simple correlation coefficient=0.454; deviation from nil correlation  $t=8.168$ ,  $P<0.0001$ ), this decrease in fructosamine levels could be explained by the decrease in albumin levels which does occur in the study subjects with age (simple correlation coefficient=-0.410; deviation from nil correlation  $t=-7.21$ ,  $P<0.0001$ ).



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Figure 4.3: histogram of fructosamine levels in normal subjects.



The serum fructosamine concentration was measured in 23 of the previously undiagnosed diabetic subjects (median = 2.15 mmol/l; range = 1.6 to 3.45 mmol/l) and in 48 subjects with IGT (median = 1.74 mmol/l; range = 1.4 to 2.13 mmol/l).

The percentile distribution of fructosamine concentrations in normal subjects is given in Figure 4.4, together with the distribution of values from the subjects with abnormal glucose tolerance; 2 diabetic subjects had fructosamine levels below the 70th percentile (1.60 and 1.67 mmol/l). By extrapolating from the 264 normal subjects to all 661 normal subjects, and including IGT subjects in the non-diabetic group, the predictive values of the fructosamine level to distinguish from diabetic and non-diabetic subjects were calculated. The IGT group included 3 subjects who had an initial MOGTT result greater than 11.0 mmol/l but were classified as IGT after second MOGTT (in other surveys they would probably have been classified as diabetic); their fructosamine concentrations were 1.73, 1.89, 1.95 mmol/l.

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Figure 4.4: table of normal fructosamine distribution and the distribution of subjects with abnormal glucose tolerance.

	Percentiles for normal glucose tolerance subjects					
	70	80	90	92	95	99
Normal subject fructosamine (mmol/l)	1.73	1.76	1.82	1.86	1.92	2.15
Diabetics above percentile (Number) <sup>a</sup>	21	21	21	20	17	13
Sensitivity (%)	91	91	91	87	74	57
Predictive +ve values for diabetes (%)	8.5	12	21.7	23.5	32.2	66.3
-ve	99.6	99.6	99.7	99.5	99.1	98.6
IGT subjects above centile (Number) <sup>b</sup>	27	22	14	12	5	0

<sup>a</sup> 2 diabetics had fructosamine values of 1.60 and 1.67 mmol/l.

<sup>b</sup> 21 IGT subjects had fructosamine values less than 1.73 mmol/l

All patients had albumin levels within the normal range (35 - 55 g/l). This normal albumin range was taken from the normal range for the Leicester hospitals, but was the same as the normal range in a previous survey of the elderly at home [209]. A normal albumin level was important since previous work had shown that the fructosamine level decreases as the albumin level decreases below 30 g/l [202,210]. Examining results from all subjects, there was a strong correlation between the fructosamine level and albumin (simple correlation coefficient=0.52; t test for difference from zero correlation  $P<0.0001$ ) and a weaker correlation for total protein (simple correlation coefficient=0.25; t test for difference from zero correlation  $P<0.05$ ), reflecting the fact that albumin is one of the main plasma proteins contributing to fructosamine. This relation between fructosamine and albumin has been previously noted in diabetic and non-diabetic subjects with normal and low albumin levels [211,212]. Some have recommended applying a correction factor for albumin level, but in Tanzania this did not make the fructosamine any better at detecting diabetes [205], and in Melton, the

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fructosamine worked well without any correction. Many other factors including time of day, lipid concentration, and particularly blood glucose level affect the fructosamine level [213], which is probably why the normal range is so wide.

#### **4.8: the value of fructosamine in diabetes detection.**

These results show that using the 95th percentile (1.92 mmol/l) as a cut off point, fructosamine achieves a sensitivity of 74%, predictive value of positive test of 32.2%, and predictive value of negative test of 99.1%, and if the 90th percentile (1.82 mmol/l) is used the sensitivity is 91%, predictive value of positive test 21.7%, and predictive value of negative test 99.7% but at the expense of specificity naturally.

These results are better than in my interim report [214] where the 95th percentile was slightly lower at 1.90 mmol/l and a sensitivity of 60% was found. This improvement is due to increasing the number of subjects studied. The interim normal range was derived from only 184 normal subjects and had to undergo logarithmic transformation to produce a normal distribution, which minimises the difference between greater values and possibly makes it more difficult to accurately define the upper normal limit. However, the upper normal limit was approximately the same on both calculations, and the improvement is due to the number of diabetic subjects detected increasing from 10 to 23, and these subjects having a higher fructosamine concentration.

The results from this study show a better overall performance than three other studies [195,196,203], despite preselection of subjects which should improve the performance of the test [198].

Two previous studies used fructosamine in population based screening surveys; one found less sensitive results in elderly Dutch with a sensitivity of 47% at a specificity of 92% [28], although patient recruitment details and results are scanty; since the specificity of a test is the proportion of true negatives correctly identified (see Figure 4.5), the specificity of a cut off value is approximately equivalent to

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the percentile of that normal value (the IGT subjects alter the result slightly) and thus the corresponding sensitivity in Melton was 87% (Figure 4.4).

Figure 4.5: sensitivity and specificity of a test [198].

Contingency table of results from a test:			
		Gold Standard test	
		+ve	-ve
New Screening test	+ve	a	b
	-ve	c	d

Sensitivity of new test =  $a/(a+c)$   
 Specificity of new test =  $d/(b+d)$   
 Predictive value of +ve test =  $a/(a+b)$   
 Predictive value of -ve test =  $d/(c+d)$

On examining Moslem Asians of all ages in Tanzania, a sensitivity of 19% at a specificity of 99% [205] was found.

Several factors may have improved the discriminatory power of serum fructosamine in the Melton study. The tests were done in the morning, minimising the diurnal variation and since the subjects rested during the MOGTT, variations in fructosamine concentration due to posture and activity were reduced [213]; none of the subjects had an acute illness and all were found to have a normal serum albumin. Although age *per se* does not effect glycosylation of other tissue proteins [215], our normal was defined for a specific sector of the population (elderly British Europids), which may well have helped, since I have shown that the normal subjects' fructosamine level did decrease with increasing age (Section 4.7). Previous workers had claimed that the glycosylated haemoglobin increased with age [216,217], but this was most likely due to their elderly subjects having abnormal glucose tolerance, for which they did not test. In this study the diagnosis was confirmed by a repeat MOGTT reclassifying 3 subjects as IGT who would have been labelled as diabetic otherwise. If these 3 subjects are classified as diabetic, it reduces the sensitivity of the fructosamine test

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slightly (95th percentile sensitivity 66.7%; 90th percentile sensitivity 85%), and this may be a factor in the lower sensitivity of other studies.

Thus there are several factors reducing variation from other causes which improve the discriminatory power of the test; however, many of these factors applied to the study in Tanzania [205], which had considerable overlap between normal and diabetic fructosamine values. One reason for this difference in results might be that in Tanzania, the fasting blood was used for fructosamine assay, whereas in our study, the 2 hour post glucose load sample was used; however, fructosamine values in the fasting and 2 hour serum samples have previously been shown to be equivalent [218]. The Tanzanian study included subjects of all age groups; the normal range was derived from half the normal subjects in each age group which one would expect to introduce a bias towards the more numerous younger subjects, whilst one would expect the diabetes to be commoner in the older subjects. Perhaps these Tanzanians also had other illnesses or poor nutrition which could affect their fructosamine level. One notable difference is that of the 994 Tanzanians tested, 228 had IGT; the fructosamine levels in patients with IGT overlapped considerably with those of normal glucose tolerance and diabetes, thus reducing the predictive value of the test. However, the Tanzanian normal range was defined on normal subjects, and this still does not explain why only 6 of the 32 new diabetic Tanzanians had an elevated fructosamine; perhaps, as the authors state, the non-diabetic Moslem Asian Tanzanians have higher blood glucose levels than subjects from areas with a low prevalence of glucose intolerance causing an elevated normal range. This raised blood glucose in the normal Tanzanian group could be dietary in origin, rather than racial, since an Asian diet has been found to produce higher blood glucose levels than a British diet [219]. Finally, the Tanzanian study had a predictive value for positive test of 41% which is reasonably good, and perhaps the authors should have adjusted their screening cut-off level to increase the sensitivity, at the expense of specificity.

It is odd that I have found fructosamine to be this sensitive since it is more closely related to the fasting plasma glucose level than the 2 h plasma glucose level

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[197,202], and the same applies to the HbA<sub>1</sub> [186,192,218]; as previously discussed in Section 4.2, the FPG is a poor test.

Thus the fructosamine concentration has been found to be a reasonable tool for detecting diabetes in the elderly of Melton Mowbray, but this depends not only on the survey method, but also on the characteristics of the study population. It is particularly important to define the normal range for the study population since the normal upper limit for serum fructosamine level varies greatly from 1.18 mmol/l in Tanzania [205], to 3.12 mmol/l in Kawerau [206]. The fructosamine level could prove useful as a simple screen for a population to select a sub-group in whom a GTT would be worthwhile. Because of the way diabetes is presently defined, fructosamine does not replace the glucose tolerance test, although some would argue that the GTT itself is not a particularly good test [114]; the GTT, however, is the best available test, with the only other "cast-iron" method being to wait several years for the development of overt diabetic symptoms or specific complications, as in the original surveys [85,87-89].

As a tool for detecting Impaired Glucose Tolerance, serum fructosamine concentration was insensitive (95th percentile cut off, sensitivity 10%; 90th percentile cut off, sensitivity 29%) as in other studies using fructosamine [196,197,202,205] and HbA<sub>1</sub> [117,192,194,195-197]. However, on a population health care basis, one does not need to identify those with IGT, since their management would be to follow the healthy diet and lifestyle recommended for the whole population.

#### **4.9: the use of glycosylated haemoglobin in the Melton survey.**

The use of glycosylated haemoglobin was very briefly investigated in the Melton survey; the new diabetic subjects, and the next normal subject of same age and sex had their HbA<sub>1</sub> measured on an EDTA blood specimen taken at the time of the MOGTT, and assayed using the Corning gel electrophoresis technique. The normal upper limit for this kit is 8.5% and the number of subjects with values above/below this are given in Figure 4.6.

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Figure 4.6: contingency table of glycosylated haemoglobin results (numbers of subjects).

	Glycosylated haemoglobin:	
	HbA <sub>1c</sub> < 8.5%	HbA <sub>1c</sub> > 8.5%
Subject:		
Diabetic	9	15
IGT	5	2
Normal	25	1

Thus an elevated HbA<sub>1c</sub> is a specific (91% specificity) but insensitive (63% sensitivity) test for diabetes.

#### 4.10: the use of urinalysis in the Melton survey.

The use of urinalysis was also studied with subjects collecting a random urine specimen, generally in the early morning since the MOGTTs were performed in the morning. The urine was tested for glycosuria with BM-test-5L strips (Boehringer Mannheim, Lewes, Sussex, UK), and 13 of 25 subjects tested had glycosuria. Figure 4.7 shows the number of new diabetic subjects with glycosuria of any degree compared to random normal (n=225) and IGT subjects (n=20); these were the subjects who were examined in greater detail in Chapter 5.

Figure 4.7: contingency table showing prevalence of glycosuria (numbers of subjects).

	Urinalysis:	
	No glycosuria	Glycosuria
Subject:		
Diabetic	12	13
IGT	17	3
Normal	213	12

Thus the urinalysis sensitivity (52%) and specificity (94%) are only slightly worse than the results using the HbA<sub>1c</sub>.

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These results were obtained using BM-test-5L/Nephur stix from Boehringer Mannheim; do the various urine testing strips perform similarly? To answer this question, standard glucose solutions were made up and tested by two independent observers using different types of urine testing strips; the observers obtained the same results which are recorded in Figure 4.8.

Figure 4.8: readings obtained from various urine sticks for different glucose concentrations (median of 3 readings).

Urine stick	Concentration of glucose solution tested (%)							
	2	1	0.5	0.2	0.1	0.05	0.025	0.0125
Diastix	2%	0.5%	0.5%	0.25%	0.1%	0.1%	neg	neg
Clinistix	Dark	Dark	Dark	Dark	med	med	light	trace
Labstix	4+	3+	2+	1+	trace	trace	neg*	neg*
Clinitest	2%	1%	1%	0.25%	0.25%	trace	neg	neg
Nephur	55mM	55mM	35mM	12mM	5.5mM	2.8mM	trace	trace
Diabur	2%	1%	0.5%	0.2%	0.1%	0.05%	trace	neg

Note: \* although the sticks were unchanged against the colour chart provided, they had change compared to an unused stick; this change was not reproduced when de-ionised water was tested.

Thus the older Clinistix and newer Nephur test stix are most sensitive at detecting small amounts of glycosuria. It has previously been noted that Clinistix are more sensitive at detecting glycosuria than Clinitest [58,69], but apart from Diastix and Clinitest, all the sticks tested were able to detect small amounts of glycosuria.

#### 4.11: a comparison of screening methods in the Melton study.

If we extrapolate from these findings to all the elderly subjects tested with a MOGTT, we can construct Figure 4.9 showing the numbers of diabetic subjects that would be found using different screening tools. I do accept that due to this extrapolation, some of the figures, particularly for HbA<sub>1c</sub>, may be imprecise.



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Figure 4.9: calculated numbers of subjects with abnormal result if applied as a screen to all 742 Melton subjects.

	Fructosamine (mmol/l):		HbA1c > 8.5%	Glycosuria
	>1.82	>1.92		
Subject:				
Diabetic	22.8	18.5	15.6	13.5
IGT	16.3	5.8	16	8.4
Normal	66.1	33.1	25.4	35.3
Number of Diabetics missed	2.2	6.5	9.4	12.5
Number of false positives	82.4	38.9	41.4	43.7
Predictive value +ve test (%)	21.7	33.2	27.4	23.6
Predictive value -ve test (%)	99.7	99.1	98.6	98.3

Thus prescreening with fructosamine can give slightly better results than the glycosylated haemoglobin or urinalysis with a similar number of false positives (1.92 mmol/l cut off), or far better case finding ability at the expense of twice as many false positives (1.82 mmol/l cut off). The predictive values of a positive fructosamine level vary from 21.7% to 33.2%, whilst the figures for glycosylated haemoglobin (27.4%), and urinalysis (23.6%) do not differ greatly; thus a subject with a positive result is just as likely to be diabetic, whichever test one uses. The predictive values for negative tests are similar for all the different methods at 98% or more, although the fructosamine achieves the highest values; the finding that a subject with a negative test is not diabetic probably relates just as much to the low prevalence of previously undiagnosed diabetes in the study population as to the merits of the test itself.

Compared to the cost of 388 mls Lucozade (35p) and a plasma glucose estimation (reagents 4p), the cost of a serum fructosamine estimation (reagents 28p) is not excessive (1988 costs); however, the commercial charge for a glycosylated

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haemoglobin using Corning gel electrophoresis is expensive at £5.00, and the HbA<sub>1c</sub> appears only marginally better than urinalysis which is considerably less expensive at approximately 6p per test stick.

Unfortunately, there is insufficient data to examine the use of a RBG timed relative to meal. The Coventry survey [76,77] missed some diabetic subjects, who were elderly; in white subjects aged 60 to 79 years, 384 were prescreened and 11 new diabetic subjects were finally found; these findings are similar to those in Melton (25 diabetic subjects from 742 residents). Coventry was very low from a socioeconomic standard, in the lowest 12 of 5,000 electoral wards [D. Simmons, personal communication], and thus one would expect a higher than average prevalence of diabetes in Coventry [122,123]. One wonders if some of the elderly diabetic subjects have been missed. If, however, most of the diabetic subjects were found, a prescreening RBG over all ages in 3217 subjects reduced the need for a GTT from 3217 tests to 442 tests.

Since approximately 80% of elderly patients [121,221-223] see their general practitioner each year, opportunistic screening could be applied in general practice; those not seen each year are generally in good health, although their glucose tolerance status has not been examined. It is interesting to note that Andersson in Laxå, Sweden [224], has screened 85% of his 3655 local residents aged 35 to 79 in just 4 years on an opportunistic approach using random blood glucose levels. Similarly Fairley reported that opportunistic screening was the most cost effective and feasible way to screen [225]; however, neither Andersson or Fairley know how many diabetic subjects have been missed by their screening and the actual effectiveness is therefore not known.

Similarly a large glycosuria detection survey claimed that urinalysis is an effective method for screening for diabetes [134], but since effective in the context of diabetes screening means detecting as many unknown diabetic subjects as possible, this claim is unfounded since again the investigators revealed a total prevalence in subjects aged 65 to 70 of only 5.2% (95% CI 3.4-7.5%). However, each diabetic detected in this urinalysis based survey cost approximately £81 to

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#### Diabetes in the elderly.

find [134], whereas each diabetic in the Melton survey would cost approximately £900 to find.

#### 4.11: conclusions.

Investigations into the use of fructosamine in Melton show that using a 1.92 mmol/l (95th percentile of normal glucose tolerant distribution) cut off point, fructosamine achieves a sensitivity of 74% (specificity 94.6%, predictive value of positive test of 32.2%, and predictive value of negative test of 99.1%) and at a 1.82 mmol/l (90th percentile of the normal glucose tolerant distribution) cut off, the sensitivity is 91% (specificity 88.5%, predictive value of positive test 21.7%, and predictive value of negative test 99.7%), but at the expense of specificity naturally.

A glycosylated haemoglobin elevated above 8.5% has a 91% specificity but only 63% specificity.

Urinalysis for any glycosuria had a sensitivity of 52% and specificity of 94%.

Thus in Melton, the careful definition of diabetes in a fairly specific population group found the fructosamine level to be good at detecting subjects likely to have diabetes with better sensitivity and specificity than either urinalysis or glycosylated haemoglobin level.

If one was a general practitioner wishing to screen the elderly, the method which one would use would depend on how well one wished to screen, and what one could afford; however, with the new general practitioner contract of 1991 [226] funding general practitioners to run diabetic clinics, there may now be a financial incentive to discover diabetic subjects. The MOGTT is still too time consuming for routine screening of the whole population, but I would still recommend its use in individuals at high risk eg family history of diabetes, arteriopathy, obesity. For routine opportunistic screening, I would suggest that either the fructosamine or critically interpreted RBG is examined for the population under question. As discussed earlier, the ability of fructosamine to detect diabetes in Melton may relate to the diagnostic procedure and population, and cannot be extrapolated

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#### Methods of diabetes screening.

elsewhere. For use of the RBG, I would strongly suggest that its use is examined in relationship to meals just in the morning to overcome diurnal variation and to ensure that the blood sample is analysed on the day of sampling rather than being left overnight. Thus whichever method is used, it would have to be set up for each situation by performing the test and a MOGTT to a representative sample of the population being screened.

From a practical and organisational point of view, opportunistic screening with a blood glucose strip eg BM stix or ExacTech strips may have several advantages; the patient does not have to produce a urine specimen, and is merely pricked and bled; the result is almost instantaneous so that organising a MOGTT can proceed immediately rather than having to await a formal plasma glucose level.

Whichever method is used, one would have to either study its use in the local population, or be able to use the exact method from a very similar population.

It may well be from a financial point of view that regular population screening by urinalysis will yield more diabetics per pound, although half the diabetic subjects will be missed from the Melton data, and with the increased renal threshold with age, the Birmingham surveys suggest that even more of the elderly diabetic subjects would be missed [58,70](see Section 2.23). For population screening to detect diabetes on a large scale, this would probably be the most realistic method, although one would have to appreciate its limitations regarding sensitivity. For instance, if one had £900 to spend on screening, the urinalysis method from Ipswich would find 11 diabetic subjects and miss a similar number, whereas the Melton MOGTT method would probably not miss any subjects, but would find only one diabetic subject.

However, for scientific studies, the glucose tolerance test is the "gold standard" at present and should be used.

Finally, one must realise that all these tests have their false negatives; an ill elderly person could have recently developed diabetes, and be heading rapidly to death from unrecognised diabetic ketoacidosis [45].

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## Diabetes in the elderly.

### Chapter 5: features of new diabetic subjects.

#### 5.1: introduction.

The features of any new diabetic subjects discovered during the diabetic survey are of interest since they may tell us which group of the population should be targeted for screening, they may help explain some variation in international diabetes prevalence data, they may tell us the impact of undiagnosed diabetes and IGT on the population, and they may tell us whether the screening is being performed too late to prevent diabetic complications if they are already present.

Previous studies looking at the features of diabetic subjects have tended to be either surveys of a clinic population [227-229], studies of clinic populations examining specific features [176,177], or population based surveys of known diabetic subjects [40,41,230-232] which varied regarding attention to specific and non-specific complications and attention to geriatric features such as cognitive impairment. One of the many reports from Framingham [231] examined features apparent in subjects before their diabetes was discovered in clinical practice. Some studies make comparisons to a normal control group, but many do not, instead looking at factors that might be associated with complications within the diabetic patient.

Some screening surveys did report some features of the new diabetic subjects. The Rancho Bernardo surveillance program found that newly discovered diabetic subjects had raised systolic blood pressure [136], as did surveys in Bedford [233], Whitehall [233], Islington [75], and Gothenburg [27]. The Kuopio and NHANES II surveys [25,20] examined the family history of diabetes and obesity in newly diagnosed and known diabetic subjects. The Tampere survey using the fasting blood glucose found that elderly diabetics were more obese, but had similar ECGs and systolic blood pressures to normal subjects [24]. Other studies also report the effect of obesity [22,26,27], and one study documents anti-hypertensive use [27]. The Bedford survey found 6.4% of new diabetic subjects had retinopathy at diagnosis, but cataract rates were similar in diabetic and normal groups [88],

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#### Newly found diabetic subjects.

across all ages. However, the Whitehall survey found that newly diagnosed diabetic subjects were more likely to have cataracts than normal subjects [88].

6-8 years after the Whitehall survey, 21% of diabetic subjects had retinopathy, and the subjects had higher systolic blood pressures and vibration perception threshold than non-diabetic control subjects [89].

Some surveys looked at the situation from a different angle; Medalie *et al* screened Israeli civil servants to produce a cohort of 9494 normal glucose tolerant subjects who were examined and then followed up for 5 years to see who developed diabetes [234]; their results are interesting, but they used pre-IGT diabetes definition, the population was multi-racial in origin, and only 756 were aged 60 years or over.

Thus many different studies have been done and they often show that newly diagnosed diabetic subjects differ from non-diabetic subjects at the time of diagnosis, or even before. What other conditions were affecting the elderly subjects found to be diabetic in the Melton survey?

#### 5.2: method.

Thus a sub-group of those participating in the diabetic survey were examined further, if willing, during the performance of the modified oral glucose tolerance test (MOGTT). This was done either in a local clinic or, particularly in subjects aged 75 and over, at home. Subject selection was based on selecting one age group per month of fieldwork and asking all these to have a clinical examination; thus the examiner was blind to the glucose tolerance status of the subject. If my other fieldworker found a subject who might be diabetic, this subject was also examined before the final MOGTT result was known, and a similar number of subjects not thought to be diabetic were also recruited by my co-worker for further examination to confuse the clinical examiner (me). On retrospect, I should have used a different procedure to pick the subjects because the younger subjects could be examined far more quickly than the older subjects; I could have picked every  $n^{\text{th}}$  name, or numbered all subjects and used random numbers. However, since

### Diabetes in the elderly.

many of the old subjects either refused the MOGTT or accepted the MOGTT but refused the examination, it would still have been difficult to gain a large random sample of the old.

Far fewer diabetics were discovered by the screening survey than anticipated, since I was expecting a total prevalence to be about 18% as in the white Americans examined in NHANES II [20]. Thus it was necessary to include data from the spouses found to have diabetes or IGT.

Figure 5.1: number of subjects examined.

Age: sex	Diabetic subjects	IGT subjects	Normal subjects
65: male	5 ( 2)	7 ( 2)	62
65: female	2 ( 0)	2 ( 1)	70
70: male	0 ( 1)	1 ( 0)	24
70: female	3 ( 0)	3 ( 0)	21
75: male	1 ( 2)	1 ( 0)	5
75: female	1 ( 0)	1 ( 0)	6
80: male	3 ( 0)	0 ( 0)	7
80: female	1 ( 0)	0 ( 0)	7
85: male	0 ( 0)	0 ( 0)	3
85: female	3 ( 0)	2 ( 0)	6
All: male	9 ( 5)	9 ( 2)	100
All: female	10 ( 0)	8 ( 1)	110
All: both	19 ( 5)	17 ( 3)	210

Note: numbers in parentheses are spouses/neighbours, not included in main figures.

2 normal 80 year females and 1 normal 85 year female were too demented to give a full history, but could be examined.

A history was taken asking for:-

- 1) Diabetic symptoms of thirst and polyuria; weight loss and tiredness were ignored since there are many other causes of these in the elderly.
- 2) A family history of diabetes in first degree relatives.
- 3) Drug history, noting whether the agents could be considered diabetogenic (see Appendix 2) or anti-hypertensive.
- 4) Smoking habits; a smoker was considered an ex-smoker if he/she had stopped smoking cigarettes for one year.

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Newly found diabetic subjects.

- 5) A history of heavy babies (9 pounds or over at birth), if appropriate (men and nuns were not asked).
- 6) Chest pain on exercise, which is relieved by rest, whether this pain had ever lasted more than 30 minutes and whether the subject had ever had a heart attack, as recommended by the WHO [235] to seek symptoms of angina pectoris and previous myocardial infarctions.
- 7) Whether the subject had ever had a Bell's palsy or carpal tunnel syndrome.
- 8) Whether the subject had ever had a stroke.
- 9) A history of pain in the legs on exercise relieved by rest and worse uphill [235] as recommended by the WHO to elicit symptoms of intermittent claudication.
- 10) previous leg or foot ulcers.

If the patient was unable to give a history, details were taken from the carer.

The hands were examined for Dupuytren's contractures, diabetic cheiroarthropathy [236], and median and ulnar neuropathies. The subjects height (in socks) and weight (in normal indoor clothes) were measured. Blood pressure (BP) was taken lying and standing using accepted techniques [237], and a Hawksley random zero sphygmomanometer; diastolic BP was measured at phase 5; lying BP was taken after at least 5 minutes recumbency and standing BP was taken after 1 minute standing.

Visual acuities were measured with a standard Snellen chart and pinhole correction if necessary; dilated funduscopy was performed using 0.5% tropicamide. Knee and ankle tendon reflexes were sought with reinforcement if necessary and vibration sense measured with a standard 128Hz tuning fork. Foot pulses were palpated and the lower limbs were inspected for scars of previous ulcers.

Finally, a 12 lead ECG was taken, and coded by the Minnesota code [235]; a random urine sample was examined using BM-test-5 L urine multistix. If there was any haematuria or proteinuria, then a mid-stream urine specimen was sent for microbiological examination.



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### Diabetes in the elderly.

Many subjects were seen; they were predominantly from the initial main list of subjects, known as volunteers, but some were spouses, friends and neighbours, known as spouses. Subjects will be referenced as (Initials; study number; age; sex (M or F); status (Volunteer or Spouse)).

Subjects will be classified by results of glucose tolerance testing as diabetic (DM), impaired glucose tolerance (IGT), or normal glucose tolerance (NGT).

Results can be analysed comparing diabetic to non-diabetic subjects (subjects with either normal or impaired glucose tolerance), or by comparing subjects with abnormal glucose tolerance (ie diabetic and IGT subjects) to subjects with normal glucose tolerance.

It is not quite correct to aggregate the glucose tolerance categories together, since the proportions sampled are not the same eg most of the diabetics were examined, approximately half the IGT subjects, and 40% of the normal subjects, so that subjects with IGT would be over-represented in a non-diabetic group. Also the normal subjects are heavily biased towards the younger end of the spectrum, and this must be borne in mind.

Due to the low numbers involved, I will add spouses to the diabetic and IGT subjects found, but not to the normal subjects; spouses were added to the age groups at the start of their quinquennia, ie 65 to 69 year old spouses were added to the 65 year old volunteers.

I shall now consider some of the features found.

#### 5.3: diabetic symptoms.

Subjects were asked for symptoms of thirst and polyuria; weight loss and tiredness were ignored since there are many other causes in the elderly. One subject (AHo, 2404, 80, M, V) denied thirst, but when asked to explain the numerous glasses of water in his room stated that he just liked water; thus the subjects may not appreciate their thirst as a problem. Only one of the 7 subjects with symptoms had consulted their general practitioner. Symptoms are recorded in Figure 5.2.

Newly found diabetic subjects.

Figure 5.2: some features of diabetic subjects found.

Name	No	Age (yrs)	Sex	Height (m)	BMI (Kg/m <sup>2</sup> )	S <sub>x</sub> (wks)	Status	D <sub>x</sub>
THu	1124	65	M	1.53	31.18	0	V	DM
CS t	1108	65	M	1.59	24.92	0	V	DM
MAs	1140	65	F	1.6	22.66	0	V	DM
GBu	1236	65	M	1.63	29.36	0	V	DM
GLe	1232	65	M	1.68	36.49	0	V	DM
BAs	2367	65	F	1.58	31.65	0	V	DM
LWa	1157	65	M	1.66	22.86	52	V	DM
MBu	2307	70	F	1.51	32.89	104	V	DM
LDa	2435	70	F	1.54	34.58	7	V	DM
MBa	2115	70	F	1.48	32.87	12	V	DM
ECr	2022	85	F	1.61	30.48	0	V	DM
LMe	2348	85	F	1.46	28.15	0	V	DM
AHa	2298	80	M	1.65	23.51	0	V	DM
AHo	2404	80	M	1.71	28.38	0	V	DM
TVi	2169	75	M	1.76	24.21	208	V	DM
IKe	2180	75	F	1.54	21.93	52	V	DM
HNe	2424	85	F	1.51	22.37	0	V	DM
EWr	1300	80	F	1.56	29.17	0	V	DM
TPe	2244	80	M	1.85	28.05	0	V	DM
DCa	1302	73	M	1.81	23.50	0	S	DM
GFr	2257	79	M	1.67	22.95	0	S	DM
FBo	1211	77	M	1.66	32.30	26	S	DM
ALo	1030	68	M	1.64	34.58	0	S	DM
RWi	1086	69	M	1.72	29.07	0	S	DM
LPh	2274	70	F	1.54	28.25	0	V	PAGT
EJo	2413	75	M	1.75	29.39	0	V	PAGT
LCI	1181	68	M	1.64	24.17	0	S	PAGT
LKe	1250	68	M	1.71	30.78	0	S	IGT
FBr	1253	65	M	1.72	23.32	0	V	IGT
JSm	1132	65	M	1.78	28.09	0	V	IGT
EBr	1159	65	M	1.78	23.99	0	V	IGT
JAr	3170	65	M	1.77	31.60	0	V	IGT
GFr	1122	65	M	1.64	24.91	0	V	IGT
PRa	1106	65	M	1.73	29.74	0	V	IGT
WSC	1144	65	M	1.62	25.53	0	V	IGT
EWe	1028	65	F	1.57	24.75	0	V	IGT
GBr	3003	70	M	1.73	18.38	0	V	IGT
NHu	1255	70	F	1.48	25.11	0	V	IGT
WSh	1266	70	F	1.49	37.39	0	V	IGT
PBa	1246	75	F	1.54	27.41	0	V	IGT
APa	1293	85	F	1.61	23.53	0	V	IGT
MS t	1109	68	F	1.56	36.16	0	S	IGT
ECr	1309	85	F	1.52	23.37	0	V	IGT
BBe	1221	65	F	1.55	26.64	0	V	IGT

S<sub>x</sub>=duration of diabetic symptoms, F=female, M=male,  
V=volunteer from list, S=spouse/neighbour, DM=diabetic,  
IGT=impaired glucose tolerance, PAGT=previous abnormality of  
glucose tolerance (treated as IGT; see Sections 2.14, 2.18).

There was no correlation between duration of symptoms and result of MOGTT  
(Kendall's rank tau=-0.134, 1 tailed P=0.18).

There was no sex difference regarding the presence of symptoms (2 tailed Fisher's  
exact P=0.393), but of 16 subjects aged under 78 years, 7 had symptoms and of the  
8 subjects aged over 78, none had symptoms(2 tailed Fisher's exact P=0.0095).

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### Diabetes in the elderly.

The Tampere screening survey of octogenarians [24] also found that none of 19 new diabetic subjects had symptoms of diabetes.

Figure 5.3: contingency table relating symptoms of polyuria/polydipsia to glycosuria (numbers of subjects).

	Glycosuria:	
	Present	Absent
Symptoms:		
Present	3	4
Absent	10	7

There was no association (Figure 5.3) between presence of symptoms and presence of glycosuria (2 tailed Fisher's exact  $P=0.66$ ).

There was no difference in GTT result between those with symptoms (median=14.3 mmol/l) and those without symptoms (median=16.6 mmol/l) (2 tailed Mann-Whitney U test  $P=0.23$ ).

Overall, 7 of the 24 new diabetic subjects admitted to thirst and polyuria, as did 5 of 220 normal glucose tolerance control subjects. Not surprisingly one can show an association between symptoms and diabetes (2 tailed Fisher's exact  $P<0.0001$ ). These 5 non-diabetic symptomatic subjects were all women aged 65, 65, 65, 70, and 85; their MOGTT results were 7.1.mmol/l or less and none had glycosuria, family history of diabetes, heavy babies, or other biochemical cause of polyuria/polydipsia.

Looking at the UK general population at all ages, it was found that the elderly were more likely to know the symptoms of diabetes than the young [238].

Questioning newly presenting diabetic subjects of all ages at a diabetes centre, revealed that only 39% noticed symptoms of their diabetes, but 80% had symptoms when directly questioned [239]. Thus people might know the symptoms of diabetes, but may still not appreciate their presence in themselves.

Recent work in Leicester in a diabetes detection drive [240] found that only 23 of 50 subjects with an elevated random plasma glucose greater than 6.5 mmol/l (out

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#### Newly found diabetic subjects.

of 383 subjects of all ages tested) had positive American Diabetes Association screening questionnaire for diabetic symptoms, and in subjects with random plasma glucose below 6.5 mmol/l 17% had thirst, and 31.5% had frequent micturition; even though these random plasma glucoses do not accurately define the subjects glucose tolerance status, this study shows how unreliable symptoms can be. Matters have not changed a great deal since 1920 when Spence noted that diabetes may be asymptomatic [64].

The elderly in the Melton study were specifically asked for diabetic symptoms, and the symptoms were still infrequent, possibly because I was picking the subjects up at an earlier stage than normal, or perhaps the elderly do not appreciate their symptoms, and neither do the younger subjects [239].

Thus a history of thirst and polyuria suggests diabetes, but elderly subjects, particularly octogenarians, may very well be asymptomatic.

#### 5.4: height and weight.

The first measurements made on the subjects were height and weight. The subjects height (in socks) with the subject looking forward was measured using a purpose built height measuring device constructed from a steel tape measure and spirit level (see Appendix 3). This gave results within 0.005 m of a traditional stadiometer, but was portable and economic; it appeared better than the cardboard cut-out measure in the British heights and weights manual [241]. Spring bathroom type scales were used to weigh the subjects (in normal indoor clothes) since again these were portable and accepted to be the only feasible method [241]. The body mass index (BMI) was calculated as traditional ie weight/height<sup>2</sup> [242], and the results for normal subjects are given in Figure 5.4 by age and sex.

#### Diabetes in the elderly.

Figure 5.4: body mass index and heights of normal subjects.

Age / sex	n	BMI (kg/m <sup>2</sup> ) :		Median Height (m)
		mean (1SD)	median	
65 /Male	62	26.8 (3.8)	26.4	1.72
65 /Female	72	25.3 (3.9)	25.0	1.59
70 /Male	24	25.6 (3.9)	25.1	1.68
70 /Female	21	26.6 (4.3)	25.2	1.57
75 /Male	5	26.7 (4.1)	27.3	1.68
75 /Female	6	29.1 (4.6)	29.5	1.535
80 /Male	7	25.3 (3.5)	27.1	1.71
80 /Female	4	24.6 (5.9)	26.9	1.55
85 /Male	3	26.4 (2.0)	25.8	1.68
85 /Female	5	23.0 (4.9)	21.5	1.545

The BMI for each age/sex group is remarkably similar although the 75 year old females are slightly heavier and the 85 year old females slightly lighter. These BMIs are higher than the BMIs obtained on British elderly in 1972 [209], and in the French more recently [243].

It would be interesting to see if the new diabetic subjects were heavier than expected, and thus each diabetic subject, both volunteers and spouses, was scored (Figure 5.2) as to whether they were heavier or lighter than the median BMI for their age/sex group. Of the 24 new diabetic subjects, 15 had heavier BMIs than their appropriate median value; the possibly high median BMI in normal 75 year old females had no effect on the result but one 85 year old diabetic female (HNe, 85, F, V) would have changed from heavy to light if her groups median was changed to 23 or more. Expecting half the diabetic subjects to be above the median weight and half below purely by chance, the BMIs obtained did not differ from this (2 tailed Fisher's exact P=0.561).

Using the same process on subjects found to have IGT (Figure 5.2) reveals 11 subjects exceeding their appropriate median weight out of 20 subjects which is not significant.

Accepting that I have got a moderate number of normal indices for only subjects aged 65-74 years, I repeated the above for sexes combined for just these age groups, and the trend for higher BMIs with diabetes or IGT was again not

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Newly found diabetic subjects.

significant (diabetes 9/13 heavy, 2 tailed Fisher's exact  $P=0.252$ ; IGT 9/16 heavy, 2 tailed Fisher's exact  $P=0.795$ ).

Thus I am unable to demonstrate a higher BMI in the newly diagnosed diabetic subjects in Melton, despite this association in other surveys [20,22,25-27,231]; this might be because of the small numbers of subjects in Melton, or because obese subjects are recognised to be at increased risk of diabetes and already diagnosed.

I was rather dubious about the recent findings of DRR Williams *et al* relating short height and diabetes [143,244,245], and so were others [246] but I examined the heights of the Melton subjects. Males without diabetes or impaired glucose tolerance at all ages had similar heights to the 65 year old men, whereas after 70 years, normal females were significantly shorter than the 65 year old normal females, presumably due to osteoporosis; I will limit analysis to these age groups. Since I am trying to confirm DRR Williams' findings, I will use one tailed tests to compare the heights of subjects with differing glucose tolerance.

91 normal females aged 65 to 70 years had median height 1.58 m (range 1.42 to 1.78 m). There were 5 new diabetic females in this age group with median height 1.54 m (range 1.48 to 1.6 m). There was a significant difference between the heights of these two groups (1 tailed Mann-Whitney U test  $P=0.041$ )

101 normal males aged 65 to 85 years had median height 1.70 m (range 1.48 to 1.87 m), and there were 14 new diabetic males with median height 1.65 m (range 1.53 to 1.85); there was no difference between the heights of these two groups (1 tailed Mann-Whitney U test  $P=0.098$ ). However, diabetic males aged 65 years from the main list of subjects (median height 1.63 m; range 1.53 to 1.68;  $n=5$ ) were shorter than older diabetic males (median height 1.71 m; range 1.64 to 1.85;  $n=9$ ), significantly so (2 tailed Mann-Whitney U test  $P=0.033$ ). Furthermore, the 65 year diabetic males were all shorter than normal males (1 tailed Mann-Whitney U test  $P=0.005$ ), but the older diabetic males were similar to normal males in height (Mann-Whitney U test 1 tailed  $P=0.41$ ).

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### Diabetes in the elderly.

Using both sexes aged 65-74 years, scoring diabetic and IGT subjects as above/below the median height of normal subjects, and comparing their heights to the expected number above/below the median, 10 of 13 diabetic subjects were less than median height (1 tailed Fisher's exact  $P=0.054$ ), but only 9 of 16 IGT subjects were below median height (1 tailed Fisher's exact  $P=0.415$ ).

I accept that these are small numbers, but they tend to confirm DRR Williams' findings in 65 year old subjects. The relationship is not seen in older subjects; this difference could be due to a cohort effect, or perhaps this is a survivor effect with the short people dying from diabetes and ischaemic heart disease [247] in their late 60s, leaving taller survivors. 20 years before the Melton survey and the work of DRR Williams, the Whitehall study showed that diabetic subjects were short for their age, but only in subjects aged 40-45 [248]; thus there may be some factor operating on the cohort born around 1925 to 1935. There is the interesting possibility that low height and future abnormal glucose tolerance are related to low size at birth, and that this phenomenon is independent of social class [249].

As Williams *et al* point out [143], no one previously has been very interested in height alone, so that although figures for BMI and social class exist, tending to increase with lower social class [241], I cannot find any similar figures for height and social class; investigators tend to concentrate on BMI, triceps skin-fold thickness and other more difficult measurements than the simple height [249a].

Finally, the elderly tend to lose height as their spines collapse and become kyphotic [243], and perhaps further work should use the armspan instead of the height, which is more constant as the subjects age and gives results closer to other anthropometric measurements than the height [250,251], particularly since some evidence shows that diabetes is associated with osteoporosis [252].

Newly found diabetic subjects.

#### 5.5: heavy babies.

The next interesting question relates heavy babies (over 9 lbs birth weight) and future diabetes (Figure 5.5).

Figure 5.5: glucose tolerance status and weight of offspring (numbers of subjects).

Babies	Normal glucose tolerance	Impaired glucose tolerance	Diabetic
Heavy	9	0	2
Normal	78	5	5
None	20	4	3
Don't know	3	0	0

There was no association between newly diagnosed diabetes and a previous history of heavy babies when comparing diabetic subjects to normal glucose tolerant subjects (2 tailed Fisher's exact  $P=0.189$ ), or on any other comparison. There was no association between having had children comparing diabetic to normal glucose tolerant subjects (2 tailed Fisher's exact  $P=0.41$ ).

It is well recognised in the textbooks that subjects with heavy babies should be followed up to see if they become diabetic [253]. In a huge long term follow up study, subjects with heavy babies and control subjects with normal weight babies had GTTs at 20 to 27 years post partum [254]; this revealed that 6.7% of the mothers of heavy babies developed diabetes over the 2 decades and this rate was 6 times that of the mothers of normal weight children. However, the mothers in both the study group and control group that became diabetic were all also obese and more likely to have a family history of diabetes than the subjects that did not develop diabetes; the report does not state whether the future diabetic women were also overweight when they delivered their babies. Thus although several factors may be interacting here, heavy babies are a marker for future NIDDM, and it appears that these subjects are getting diagnosed before they become elderly, possibly because this association is well known.



## Diabetes in the elderly.

### 5.6: family history of diabetes.

There was no association between a history of diabetes in siblings or parents and diabetes (Figure 5.6) comparing diabetic to normal glucose tolerant subjects (2 tailed Fisher's exact  $P=0.728$ ), and there was no sex difference in diabetic subjects regarding a positive family history (2 tailed Fisher's exact  $P=1.0$ ).

Figure 5.6: glucose tolerance status and family history of diabetes (numbers of subjects).

	Normal glucose tolerance	Impaired glucose tolerance	Diabetic
<b>MEN:</b>			
Yes	3	2	2
No	102	9	12
<b>WOMEN:</b>			
Yes	19	1	1
No	88	8	9
Don't know	3		

Although a family history of diabetes is a strong risk factor for diabetes, in NHANES II [20] and Kuopio [25], it was associated with known rather than newly diagnosed diabetes.

Follow up of subjects from Bedford and Whitehall with IGT showed that a positive family history of diabetes was not associated with future development of diabetes [110,111].

The previous findings that a family history is associated with known diabetes but not newly diagnosed diabetes in Melton suggests that subjects with a positive family history are being diagnosed earlier, either by physicians who recognise the association, or by the patients themselves who get diabetic knowledge and testing equipment from their affected family members; however, it has been noted that subjects with diabetic relatives are no more likely to be aware of the significance of diabetic symptoms than subjects without diabetic relatives and do not generally appreciate their increased risk of diabetes [255].

Newly found diabetic subjects.

#### 5.7: smoking habits.

Examining just normal glucose tolerant subjects (Figure 5.7), there was a dramatic sex difference; females were far less likely to have smoked (2 tailed Fisher's exact  $P < 0.0001$ ).

Figure 5.7: contingency table of smoking and glucose tolerance status (numbers of subjects).

Glucose tolerance status (number)	Smoking habits:		
	Present	Previous	Never
DM Male (14)	2	9	3
DM Female (10)	1	3	6
IGT Male (11)	2	9	0
IGT Female (9)	1	1	7
Normal Male (101)	25	55	21
Normal Female (110)	15	38	57

Reducing the data for each sex to 2 by 2 contingency tables using various combinations of class of smoking habit and class of glucose tolerance and applying a Mantel Haenszel  $\chi^2$  test to these series of two 2 by 2 tables revealed no difference in smoking habits for the different groups of subjects ( $p > 0.4$ ).

Interestingly, smoking does cluster with other cardiovascular risk factors in Californians aged 35 to 79 years [136], but the paper does not specify whether this applies to the elderly Californians within this whole group; one would suspect that diabetic subjects with a cluster of cardiovascular risk factors would not constitute a large proportion of an elderly population due to the increased risk of vascular death [256]. In younger subjects, smoking habits were similar in known diabetic and normal subjects [257], but if the smoking diabetic subjects did not survive to old age, the population would need to develop diabetes in more smokers to maintain the numbers of smoking diabetic subjects; however, in Bedford and Whitehall, smoking did not influence the development of diabetes in subjects with IGT [110,111], and in the Framingham study [231] smoking habits had no effect on the incidence of diabetes. Some known diabetic subjects smoke more once they have been to a diabetic clinic [258], and perhaps the point is not that smokers

### Diabetes in the elderly.

become diabetic, but that diabetics become smokers. 10% of smoking diabetic subjects deny that they smoke [258] and this may further cloud the picture.

Thus it seems strange that the subjects with abnormal glucose tolerance found in Melton did not have a reduced proportion of smokers. It may be that the Melton subjects were found earlier in the course of their diabetes before smoking related illnesses could take their toll, or again the lack of association may be due to small figures.

### 5.8: strokes.

Subjects were asked if they had ever had a stroke or a weakness down one side. One subject (JMo, 65, F, V) had had a hemiparesis due to a meningioma, one subject later volunteered a classic history of amaurosis fugax (ACI, 65, M, V), and one subject had a history of subjective alteration of sensation down one side (EWe, 80, F, V); these subjects will not be included as strokes. There were no subjects with transient ischaemic attacks. 9 subjects had had previous strokes and they were all on the main subject list (Figure 5.8).

Figure 5.8: details of subjects with previous hemiparesis.

Subject	Age	Sex	Systolic BP	AntiHT drugs	Smoke
Normal:					
WGr	65	M	126	N	N
EFr	65	M	164	N	P
MMa	80	F	160	N	Y
TTu	75	M	140	Y	N
IGT:					
JAr	65	M	180	Y	P
ECr	85	F	140	N	N
Diabetic:					
LDa	70	F	185	N	P
ECr	85	F	156	Y	N
TVi	75	M	176	N	N

Note: M=male, F=female, N=no, Y=yes, P=previous.

#### Newly found diabetic subjects.

There is no obvious age or sex distribution of the strokes, but since there was a larger proportion of diabetic subjects in the older age groups examined, the data were converted to a series of three 2 by 2 contingency tables by glucose tolerance status and presence/absence of previous stroke for each decade of age (Figure 5.9).

Figure 5.9: contingency tables of strokes and glucose tolerance status (numbers of subjects).

Age	Previous stroke	Glucose tolerance:		
		Normal	IGT	Diabetic
65 - 69	Yes	2	1	0
65 - 69	No	130	11	8
70 - 79	Yes	1	0	2
70 - 79	No	55	6	6
80 - 85	Yes	1	1	1
80 - 85	No	22	1	6

For new diabetes versus normal glucose tolerance, there was no significant difference (Mantel Haenszel  $\chi^2=3.1$ ,  $P=0.079$ ; odds ratio=6.01, 95% CI 0.82-44.3).

For any abnormality of glucose tolerance (DM+IGT) versus normal glucose tolerance, there was a significant difference, (Mantel Haenszel  $\chi^2=5.11$ ,  $P=0.024$ ; odds ratio=5.91, 95% CI 1.27-27.53).

For diabetes versus non-diabetes (normal glucose tolerance and IGT), there was no significant difference, (Mantel Haenszel  $\chi^2=1.93$ ,  $P=0.16$ ; odds ratio=3.97, 95% CI 0.57-27.63).

Prospectively following up subjects from the Whitehall study [259], revealed that subjects with a GTT result above the 95<sup>th</sup> centile (5.4 mmol/l) were significantly more likely to develop a stroke than subjects with lower GTT results; unfortunately insufficient diabetic subjects were found to render the trend for increased risk of stroke in them to be statistically significant.

However, prospectively following subjects screened with a fasting blood glucose [260] failed to reveal any increased risk of stroke with higher FBGs, which may well be further evidence that the FBG is a poor test (see Sections 2.3, 4.3).

### Diabetes in the elderly.

The Rochester Epidemiologic Project closely monitors its population for diabetes; here diabetic subjects are 1.7 times more likely to develop a stroke than subjects not known to be diabetic ( $p < 0.01$ ) [261].

Thus following known diabetic subjects reveals an excess of cerebrovascular disease; the other approach is to look at stroke victims regarding glucose tolerance status. A case control study of 400 stroke subjects revealed that 10.8% had known diabetes compared to only 4.3% in age/sex matched controls (2 tailed Fisher's exact  $P = 0.00068$ ) [262].

On examining 86 subjects presenting with acute strokes, average age 73 years, 6 were known to have diabetes and a further 24 had an elevated glycosylated haemoglobin level [263]; if 30 of these 86 stroke victims are diabetic, that is a greater prevalence of previously undiagnosed diabetes (35%, 95% CI 25-46) than in the Melton diabetes survey. These figures are very similar to a smaller study from Leicester where elderly stroke survivors who were not known to be diabetic had two GTTs 12 weeks apart and 37.5% (95% CI 15.2-64.6%) fulfilled strict WHO criteria for diabetes [264].

Thus the data from the Melton study support the findings from the Whitehall study that subjects with higher results from the GTT are more prone to cerebrovascular disease, although the Melton study was retrospective and the Whitehall study prospective regarding the cerebrovascular disease; both studies suggest that newly diagnosed diabetes is linked to cerebrovascular disease, but both have insufficient numbers of new diabetic subjects to prove this. Thus early in the course of abnormal glucose tolerance, there is an association with macrovascular disease; "chicken or egg or neither?" as RJ Jarrett asked [265].

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Newly found diabetic subjects.

Jarrett pointed out in an extensive review in 1984 3 facts shown by many studies:-

a: duration of NIDDM has no effect on the incidence of vascular events.

b: subjects prior to developing NIDDM had higher blood pressures and cholesterol levels.

c: subjects with NIDDM pass through a period of IGT and IGT is as much a risk factor for macrovascular disease as NIDDM.

Thus he concluded that " certain metabolic milieux predispose to the development of cardiovascular disease and/or diabetes". It now appears that insulin resistance may be an important factor for this adverse metabolic milieux [266]. The presence of hypertension in the Melton survey is discussed in Section 5.18.

#### **5.9: entrapment mononeuropathies.**

Subjects were asked for a previous history of carpal tunnel syndrome (CTS) and Bell's palsy and the hands were examined for the muscle wasting and weakness of ulnar and median neuropathies.

One subject gave a history of Bell's palsy (JBo 70, F, V) and she had normal glucose tolerance.

Four subjects (all on main subject list) gave a history of previous carpal tunnels; 2 were male aged 65 and 70 with normal glucose tolerance and 2 were female aged 70 and 85 with newly diagnosed diabetes.

On hand examination, two male subjects had carpal tunnel syndromes with classical wasting and weakness of abductor pollicis brevis; one was 80, on the main list and normal glucose tolerant whilst the other was 73, a neighbour, and diabetic.

Thus carpal tunnel syndromes are occurring in both sexes at all ages.

#### Diabetes in the elderly.

Figure 5.10: subjects with carpal tunnel compression (numbers of subjects).

Glucose tolerance status (number)	Number with CTS:	
	History	Exam
Diabetes (24)	2	1
IGT (20)	0	0
Normal (211)	2	1

Comparing normal glucose tolerant subjects to new diabetic subjects, a history or clinical finding of CTS is associated with diabetes (2 tailed Fisher's exact  $P=0.0155$ ; odds ratio 9.65, 95% CI 1.47-66.68). A previous history of CTS was not quite associated with diabetes (2 tailed Fisher's exact  $P=0.0533$ ), and finding a previously undiagnosed case of CTS was definitely not (2 tailed Fisher's exact  $P=0.195$ ).

Previous investigators using a medical records linkage system in Rochester where there is continuous surveillance for diabetes mellitus, revealed that subjects with carpal tunnel syndrome were 2.3 times more likely to have known diabetes mellitus than the general population [267].

Thus, overall, the association between carpal tunnel syndrome and diabetes is confirmed in the Melton study.

One subject (EBa 65, F, V) had an ulnar neuropathy, and normal glucose tolerance but died one month later. This lady was aware of her terminal carcinoma of breast, and her participation in this study for her was futile; nonetheless she joined in demonstrating the willingness of some elderly in Melton to participate in studies.

#### 5.10: hands.

The hands were also examined for Dupuytren's contractures (by feeling for thickening of the palmar fascia) and diabetic cheiroarthropathy (by the prayer sign) [236]. No subjects had cheiroarthropathy. Six subjects (all on the main subject list) had Dupuytren's contractures and all had normal glucose tolerance. Thus these hand abnormalities which are recognised to accompany diabetes [268-270] are not present to a significant degree at this early stage in these small numbers of

Newly found diabetic subjects.

diabetic subjects revealed by screening the elderly of Melton. Again this could be a type 2 error, or it may be that these hand complications need time to develop; their prevalence increases with the duration of diabetes [268].

#### 5.11: peripheral neuropathy.

Vibration was examined using a standard 128 Hz tuning fork and recorded as diminished if the subject could not reliably distinguish it at the medial malleolus of the ankle. Ankle jerks were elicited with a standard Queen's Square tendon hammer and the ankle reflexes were recorded as decreased if they were absent or needed reinforcement to obtain them. These commonly used methods were used for precisely the reasons which make them common, they are simple, inexpensive and portable [271], unlike a biothesiometer. The results are given in Table 5.11.

Figure 5.11: table of evidence of neuropathy in subjects of various ages and glucose tolerance (numbers of subjects).

Age (years)	Glucose tolerance status (number)	Number with:		
		↓vibes	↓AJ	Either
65	Diabetic ( 9)	0	3	3
	IGT ( 12)	1	4	4
	Normal (132)	5	6	7
70	Diabetic ( 4)	2	0	2
	IGT ( 4)	0	0	0
	Normal ( 45)	3	2	4
75	Diabetic ( 4)	0	1	1
	IGT ( 2)	0	2	2
	Normal ( 11)	3	2	3
80	Diabetic ( 4)	1	3	3
	IGT ( 0)	0	0	0
	Normal ( 14)	1	3	3
85	Diabetic ( 3)	1	1	1
	IGT ( 2)	0	0	0
	Normal ( 9)	5	3	5

↓vibes=decreased vibration sense at the ankle;  
↓AJ=decreased ankle tendon reflex.

These data were converted to a series of three 2 by 2 contingency tables by each decade of age for decreased vibration sense, decreased ankle reflex and either of these by diabetes versus normal glucose tolerance, as per strokes in Section 5.8.



### Diabetes in the elderly.

The tables were analysed by a Mantel Haenszel Chi<sup>2</sup> test and these results are shown in Table 5.12.

Figure 5.12: results of Mantel Haenszel Chi<sup>2</sup> test on neuropathy.

Evidence of neuropathy	Mantel Haenszel: Chi <sup>2</sup>	P	Odds ratio (95% CI)
↓vibes	0.041	0.8393	1.42 (0.05-42.76)
↓AJ	6.931	0.0085	4.43 (1.46-13.41)
Either	8.087	0.0045	4.20 (1.56-11.29)

↓vibes=decreased vibration sense at the ankle;  
↓AJ=decreased ankle tendon reflex.

The analysis shows that the newly diagnosed diabetic subject was more likely to have impaired ankle reflexes, or the possibility of decreased ankle reflexes or vibration sense at the time of diagnosis.

Walters *et al* in a large community survey in Poole examined the majority of diabetic subjects within their study population (1077 subjects) for neuropathy as defined by the presence of 2 or more features of neuropathy [272]; 20.5% (95% CI 17.6-23.6) of diabetic subjects aged 60 or more had neuropathy compared to 3.9% (95% CI 2.1-6.4) in a control group not known to be diabetic. Increasing prevalence of neuropathy was independently correlated to age of the subject, duration of diabetes and glycaemic control. This mammoth survey unfortunately does not give data on the prevalence of neuropathy early in the course of the diabetes.

The Rochester community surveillance program for diabetes reported that the median time from diagnosis of diabetes to onset of neuropathy was 9 years; the prevalence of neuropathy increased with duration of diabetes and worse glycaemic control [261].

Dornan's survey of elderly diabetic subjects in two general practices [40] found that 35% of the diabetic subjects compared to 21% of age/sex matched controls had decreased vibration sense (2 tailed Fisher's exact P=0.056), but again this finding was in a group of subjects with mean disease duration of 9 years.

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#### Newly found diabetic subjects.

In the Whitehall survey, diabetic subjects detected by a screening survey when under the age of 65 years had significantly impaired vibration perception threshold compared to normal subjects after just 5 years after diagnosis by screening [89].

Using more sophisticated tests for neuropathy, does also demonstrate decreased nerve conduction velocities at time of routine diagnosis of NIDDM compared to subjects not known to be diabetic [272a].

Overall, more of the elderly Melton subjects had normal ankle reflexes and vibration sense than classically believed [273]; however, the previous studies on this topic generally examined hospital inpatients, Chelsea pensioners and subjects receiving financial aid who were presumably unwell and not representative of the general population; findings from community volunteers are not dissimilar to the findings in Melton [273]. Interestingly, one study examining healthy young and old found no difference in objective measurement of neuropathy with ageing using electric current perception thresholds [274], which correlates better with the clinical extent of neuropathy than vibrometric or nerve conduction testing; the use of vibration thresholds as measured by a biothesiometer is unreliable in the elderly with a high coefficient of variation [275].

Thus although many investigators would use stricter criteria or more sophisticated equipment to diagnose neuropathy, the methods which I used, which were the same for all subjects, and demonstrated that diabetic subjects revealed by screening have evidence of a specific complication at the time of diagnosis.

#### 5.12: eyes.

Dilated funduscopy was performed in the subjects examined, after visual acuity measurement; this was often performed in the patients' home.

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#### Diabetes in the elderly.

##### **5.13: diabetic retinopathy.**

Background retinopathy (microaneurysms) was found in one newly diagnosed diabetic subject (MBa, 70, F, V), but no other subjects had diabetic retinopathy. This prevalence of retinopathy is not significantly different to the 10.5% (95% CI 9.3-11.8) of newly diagnosed elderly diabetic patients at the Birmingham outpatient clinic [276] examined using normal clinical methods. The UK prospective diabetes study examined younger new diabetic subjects using examination and retinal photography and found that 23.8% of patients had retinopathy, and that subjects with retinopathy were older than those without [277], which is most likely a reflection of more intensive examination by both ophthalmoscope and retinal photograph.

##### **5.14: retinal vascular disease.**

Retinal artery occlusion (RAO) (2 central, 1 branch) was found in 3 subjects (THu, 65, M, V; CSt, 65, M, V; MBu, 70, F, V) who all had newly diagnosed diabetes; there was a strong association between RAO and new diabetes comparing diabetic to normal glucose tolerance subjects (2 tailed Fisher's exact  $P=0.00096$ ; odds ratio 68.5, 95% CI 4.16-301.04). Previous surveys of subjects with RAO [278-283] revealed an increasing prevalence of diabetes from 5% to 27% as the studies became more modern, particularly in the USA, and this probably relates to an increasing awareness of diabetes. However, all these studies omitted any form of glucose tolerance test and had no control population without RAO; the highest prevalence found was 9 of 33 Americans of all ages with RAO [281] suggesting an increased prevalence of diabetes in subjects with RAO. I can find no reference to this association, although the association between diabetes and retinal vein occlusion is well known [284]. This association between diabetes and RAO probably relates to severe vascular disease since all 3 Melton subjects with RAO had angina, 1 had had a myocardial infarction, 2 had intermittent claudication and one had had the only ischaemic foot ulcer found. It has been previously noted that those with RAO have increased morbidity and mortality

#### Newly found diabetic subjects.

from cardiovascular disease in particular, but also cerebrovascular and peripheral vascular disease [278,280,282].

Several subjects had arteriovenous nipping but no florid hypertensive changes were found.

#### 5.15: glaucoma.

3 subjects were known to have glaucoma; their eyes were not dilated; 2 had normal glucose tolerance and one had IGT. One subject had glaucomatous cupping of the optic disc and was a newly found diabetic (AHa, 80, M, V); interestingly his General Practitioner records contained a referral slip from the optician who had found raised intra-ocular pressures, but it had been neglected. There was no association between abnormalities of glucose tolerance and glaucoma comparing diabetic to normal glucose tolerant subjects (2 tailed Fisher's exact  $P=0.23$ ).

#### 5.16: senile macular degeneration.

The distinction between drusen and early senile macular degeneration is difficult, but in practice [285] it is taken as SMD if the visual acuity is 6/9 or worse for no other reason. 20 subjects had SMD (Figure 5.13), although in only 3 was it severe enough to need blind registration; in these 3 subjects, 1 was normal, 1 had IGT, and 1 had newly diagnosed diabetes; there was no association between glucose tolerance and blind registrations for SMD (2 tailed Fisher's exact  $P=0.195$ ).

Amalgamating to produce a series of three 2 by 2 contingency tables by each decade of age revealed no difference in prevalence of SMD in diabetic compared to normal subjects (Mantel Haenszel  $\chi^2=3.38$ ,  $P=0.066$ , odds ratio=3.27, 95% CI 0.92-11.56) and adding the IGT subjects to either the normal or diabetic subjects weakened the significance even further ( $p>0.09$ ). It was naturally more common in the old.

### Diabetes in the elderly.

Figure 5.13: SMD versus glucose tolerance status (numbers of subjects).

Age	Diabetic subjects	IGT subjects	Normal subjects
65	1 (9)	0 (12)	7 (132)
70	0 (4)	0 (4)	3 (45)
75	2 (4)	1 (2)	0 (11)
>79	1 (7)	1 (2)	4 (23)

(\*)= number of subjects in category (at risk).

Other surveys have found no association between SMD and diabetes [285-287]. It is interesting to note, however, that cardiovascular disease, even allowing for smoking, is weakly associated with SMD [286], and so is previous hypertension [288]; thus there might be a weak association between diabetes and SMD if one looked at a larger, older population for both diseases.

### 5.17: cataracts.

Cataracts were recorded as present if there was any opacity of the lens present, and previous extractions were noted; both were analysed together as "presence of cataract". Apart from one traumatic cataract, the fundus could also be examined in these subjects. Of the 29 subjects with cataracts, 3 had had them extracted.

Figure 5.14: number of subjects with cataracts in relation to all subjects examined (subjects with cataracts/subjects examined (numbers of subjects)).

Age / sex	Diabetic subjects	IGT subjects	Normal subjects
65/male	2/07	0/9	5/62
65/female	0/02	1/3	5/70
70/male	0/01	0/1	0/24
70/female	0/03	0/3	4/21
75/male	1/03	0/1	0/05
75/female	1/01	0/1	1/06
80/male	1/01	0/0	0/07
80/female	1/03	0/0	2/07
85/male	0/00	0/0	1/03
85/female	2/03	1/2	0/06
All/male	4/09	0/11	6/101
All/female	4/10	2/9	12/110
All/both	8/24	2/20	18/211

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#### Newly found diabetic subjects.

In normal subjects, there was no sex difference in cataract rate (2 tailed Fisher's exact  $P=0.223$ ), and there was no obvious difference with age having combined quinquennia into each decade of age ( $\text{Chi}^2=0.625$ ,  $\text{DF}=2$ ,  $P=0.732$ ).

Figure 5.14: number of subjects with cataracts in relation to subjects in age/glucose tolerance group (subjects with cataracts/subjects examined (numbers of subjects)).

Age	Diabetic subjects	IGT subjects	Normal subjects
65 - 69	2/09	1/12	10/132
70 - 79	2/08	0/06	5/056
80 - 85	4/07	1/02	3/023

However, when reduced to a series of 2 by 2 contingency tables for cataract by glucose tolerance and analysed by Mantel Haenszel  $\text{Chi}^2$  tests, there was an association between diabetes and cataracts (Mantel Haenszel  $\text{Chi}^2=7.53$ ,  $P=0.0061$ ; odds ratio=4.70, 95% CI 1.56-14.20); this was weakened slightly if the analysis was performed comparing diabetic to non-diabetic subjects (Mantel Haenszel  $\text{Chi}^2=7.33$ ,  $P=0.0068$ ), and if abnormal glucose tolerance was compared to normal glucose tolerance, the association was weakened dramatically (Mantel Haenszel  $\text{Chi}^2=4.42$ ,  $P=0.036$ ).

Thus even at this early stage in the course of their disease, diabetic subjects were more prone to cataracts than their normal glucose tolerant peers.

The American HANES I survey found that known cataracts were associated with known diabetes [289]. At the time of cataract extraction in Oxford, 8.8% of subjects were known to have diabetes and 4.2% were found to have diabetes [290], although the criteria for diabetes then would include subjects now thought to have IGT, and subjects selected for cataract extraction may not be representative of the general population of cataract sufferers. In the Whitehall survey, newly found diabetic subjects had a significantly increased prevalence of cataract [88].

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#### Diabetes in the elderly.

These surveys considered either subjects of all ages, or middle aged subjects; it is interesting to note that this association is seen in the elderly of Melton also.

One other study both examined dilated eyes through a slit lamp for cataracts, and then performed a GTT [291]; despite doing exactly the correct things to identify diabetes and cataracts, this did not show any difference in GTT result for subjects with and without cataracts, which may be because both diabetes and cataract are a disease of the elderly who formed only a small number of subjects in this study (only 133 subjects were aged 60 years or more).

Interestingly, low levels of some anti-oxidants have been found in subjects with cataracts [292,293], and these low levels occur in diabetes [294-296]. It has also been noted that subjects with cataracts are shorter than expected [297] (see Section 5.4)! Cataracts are associated with hypertension [285,289,297] (see Section 5.18). Thus diabetes and cataract seem closely linked, for whatever reason.

#### **5.18: hypertension, antihypertensive treatment, and left ventricular hypertrophy.**

Subjects' medication was examined to find anti-hypertensive medication; an agent that was indicated for hypertension treatment was scored as an antihypertensive agent, even if it may have been prescribed for another indication eg a calcium channel blocker for angina. The subjects' blood pressure was examined lying and standing as recommended [237] using a Hawksley random zero sphygmomanometer, and the subjects' electrocardiogram was recorded and examined for left ventricular hypertrophy using the Minnesota codes 3-1, 3-3 and 3-4 [235].

Hypertension is an elevated blood pressure leading to increased morbidity and mortality. It is recognised that in the elderly antihypertensive medication reduces strokes and mortality [137,298-300]; however in subjects aged over 80, "hypertensive" individuals fare better than "normotensive" individuals [301-303]. Therefore, I will only consider hypertension in subjects less than 80 years old.

#### Newly found diabetic subjects.

Since only 3 subjects had a diastolic blood pressure > 100 mm Hg without systolic >160 mm Hg compared to 57 with systolic hypertension (systolic BP > 160 mm Hg), these 3 subjects will not be included and I will consider only systolic hypertension.

I realise that a single blood pressure reading is poor at defining hypertensive subjects since the blood pressure is highly likely to decrease on subsequent readings [237].

Figure 5.15: hypertension, anti-hypertensive treatment and left ventricular hypertrophy in relation to glucose tolerance status in Melton subjects (numbers of subjects).

Subjects (number)	Evidence of hypertension:			
	Anti-HT	Sys-HT	LVH	Any
<b>Male:</b>				
65-69 Diabetic ( 7)	5	2	1	6
65-69 IGT ( 9)	1	3	0	3
65 Normal (62)	6	8	6	14
70-74 Diabetic ( 1)	0	0	0	0
70-74 IGT ( 1)	0	0	0	0
70 Normal (24)	2	8	2	10
75-79 Diabetic ( 3)	0	2	0	2
75-79 IGT ( 1)	0	0	0	0
75 Normal ( 5)	2	2	0	3
80-85 Diabetic ( 3)	2	0	0	2
80-85 IGT ( 0)	0	0	0	0
80/85 Normal (10)	3	4	0	6
<b>Female:</b>				
65-69 Diabetic ( 2)	1	0	0	1
65-69 IGT ( 3)	1	1	0	1
65 Normal (70)	11	16	3	24
70-74 Diabetic ( 3)	1	2	0	3
70-74 IGT ( 3)	0	1	1	1
70 Normal (21)	5	8	0	11
75-79 Diabetic ( 1)	1	0	0	1
75-79 IGT ( 1)	0	0	0	0
75 Normal ( 6)	3	1	0	3
80-85 Diabetic ( 4)	2	2	1	4
80-85 IGT ( 2)	1	1	0	1
80/85 Normal (13)	3	4	2	6

Sys-HT=systolic hypertension; Anti-HT=antihypertensive medication; LVH=electrocardiographic evidence of left ventricular hypertrophy.

In the normal glucose tolerant subjects, there was no association between sex and antihypertensive use, systolic hypertension, LVH, or presence of any of these



### Diabetes in the elderly.

features when reduced to a series of three 2 by 2 contingency tables by age group (Mantel Haenszel  $\chi^2$   $P > 0.1$ ).

Comparisons were therefore made between diabetic and normal subjects with the sexes combined; this also gave similar values to those obtained when the sexes were considered independently. Having any of the features of hypertension was associated with newly diagnosed diabetes (Mantel Haenszel  $\chi^2 = 7.851$ ,  $P = 0.0051$ ; odds ratio = 5.22, 95% CI 1.64-16.57), as was anti-hypertensive treatment (Mantel Haenszel  $\chi^2 = 5.402$ ,  $P = 0.020$ ; odds ratio = 3.29, 95% CI 1.21-8.99). Systolic hypertension and LVH were not associated with diabetes (Mantel Haenszel  $\chi^2$   $P > 0.1$ ).

Comparisons were made between IGT and normal glucose tolerant subjects and there was no difference between these groups regarding antihypertensive use, systolic hypertension, LVH, or presence of any of these features (Mantel Haenszel  $\chi^2$   $P > 0.1$ ).

It is known that hypertension is commoner in subjects with NIDDM than in subjects with either IDDM or presumed normal glucose tolerance [304]; the Framingham study confirmed this, and also showed that diabetic subjects were also more likely to have LVH on the ECG [305]. Many studies have shown evidence of excess hypertension in diabetic subjects detected by screening such as the Rancho Bernardo survey [136], Bedford [233], Whitehall [233], Islington [75], and Gothenburg [27].

The Framingham heart study [231] also found that systolic hypertension and diuretic use were associated with the future development of diabetes, and in Uppsala [308] systolic blood pressure was again an independent predictor of future diabetes. Interestingly, Finns with hypertension in 1986 who were normotensive in 1968 had significantly higher blood glucose levels in 1968 than their peers who were normotensive on both occasions [307]. In non-diabetic subjects, systolic and diastolic blood pressures were positively correlated with fasting insulin level and glycosylated haemoglobin level [308] when allowing for the effects of age, sex, and obesity; however, no GTTs were done to confirm

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#### Newly found diabetic subjects.

normal glucose tolerance and no glucose levels are mentioned in the report concerned. A massive cross-sectional study in Malmö examined 6956 middle aged men using a GTT, blood pressure measurement and an index of insulin resistance [309], revealing that in normoglycaemic individuals, insulin resistance was positively and significantly correlated with blood pressure; IGT subjects had marked insulin resistance using their index, as did newly diagnosed diabetic subjects, and in both these groups hypertension was extremely common.

Thus hypertension and metabolic abnormalities associated with diabetes seem to run together. It has been noted that hypertensive 50 year olds had higher, but not hypertensive, blood pressures than their normotensive peers 30 years earlier [310], suggesting that the problem starts at an early age, which ties in with the low birth weights and future diabetes and vascular disease as discussed in Section 5.4 [249].

The question now is "is it hypertension or the treatment which contributes to the development of diabetes, diabetes which contributes to the development of hypertension, or another factor, eg insulin resistance, which causes both the diabetes and hypertension?; see Section 5.19.

#### 5.19: drug treatment.

What is the role of diabetogenic drug treatment in the aetiology of diabetes in the elderly? It is generally accepted that the major diabetogenic drugs of note are the thiazide diuretics and steroids [50,311]. There are other markedly diabetogenic drugs in existence, but they are not used frequently in the elderly, such as diazoxide, and l-asparaginase. Other agents are less diabetogenic or borderline, and full details are given in Appendix 2.

Each subject's drug history was taken, and the results recorded and analysed in terms of numbers of classes of treatment to avoid the problem of patients taking compound preparations; thus subjects taking coamilofruse, or duovent inhalers or coproxamol would be counted as taking one class, but so would frusemide and amiloride or ventolin, atrovent and becotide inhalers or ibuprofen and paracetamol. I would justify this method, since I wish to use medication as an

### Diabetes in the elderly.

indicator of other illnesses, rather than how much the subjects are taking for their illness.

It was also recorded whether the subjects were taking antihypertensive treatment including all thiazide diuretics, calcium channel blockers *etc* even though they may have been prescribed for another indication. Whether drugs were major diabetogenic drugs or not was also recorded. (Figure 5.16)

Figure 5.16: number of classes of drugs and diabetogenic drugs taken by normal glucose tolerance subjects (numbers of subjects).

Age/sex	Subjects taking number of drug classes (numbers)				
	0	1	2	3	>3
65/male	39 (0)	16 (2)	5 (1)	1 (0)	1 (0)
65/female	41 (0)	16 (3)	8 (3)	1 (0)	4 (1)
70/male	14 (0)	7 (0)	2 (0)	1 (0)	0 (0)
70/female	8 (0)	6 (0)	3 (1)	3 (2)	1 (1)
75/male	3 (0)	0 (0)	0 (0)	0 (0)	2 (1)
75/female	1 (0)	1 (1)	1 (1)	2 (2)	1 (1)
80/male	3 (0)	2 (1)	1 (1)	0 (0)	1 (0)
80/female	0 (0)	4 (0)	2 (0)	1 (0)	0 (0)
85/male	2 (0)	1 (0)	0 (0)	0 (0)	0 (0)
85/female	3 (0)	1 (0)	1 (0)	0 (0)	1 (0)

(numbers in parentheses are number on major diabetogenic drugs)

Considering numbers of classes of drugs taken as 0 or greater than 0, and constructing a series of five age related 2 by 2 contingency tables for sex versus drug use, there was no effect of sex on drug taking (Mantel Haenszel  $\chi^2=3.04$ ,  $P=0.081$ ; odds ratio=1.71, 95% CI 0.94-3.13).

Considering Figure 5.18 as ages 65, 70, and 75 or more, and drug classes as 0, 1, 2, and greater than 2 (to give adequate cell sizes), then there is a difference in drug use with age ( $\chi^2=14.0$ ,  $DF=6$ ,  $P=0.03$ ); there is no difference between 65 and 70 year olds but these age groups differ significantly from 75 years old or older ( $\chi^2=11.7$ ;  $DF=3$ ;  $P=0.008$ ).

Thus the data for subjects with abnormal glucose tolerance will be charted by age group but not by sex (Figure 5.17).

### Newly found diabetic subjects.

Figure 5.17: number of classes of drugs and diabetogenic drugs taken by abnormal glucose tolerance subjects (numbers of subjects).

Age/GTT (number)	Subjects taking number of drug classes (numbers)				
	0	1	2	3	>3
<b>Diabetic:</b>					
65-69 (9)	1 (0)	2 (0)	5 (2)	1 (1)	0 (0)
70-74 (4)	2 (0)	1 (0)	0 (0)	1 (1)	0 (0)
75-79 (4)	2 (0)	2 (1)	0 (0)	0 (0)	0 (0)
80-85 (7)	2 (0)	3 (2)	0 (0)	1 (1)	1 (1)
<b>IGT:</b>					
65-69 (12)	6 (0)	2 (0)	2 (1)	2 (1)	0 (0)
70-74 (4)	4 (0)	0 (0)	0 (0)	0 (0)	0 (0)
75-79 (2)	2 (0)	0 (0)	0 (0)	0 (0)	0 (0)
80-85 (2)	0 (0)	1 (1)	1 (0)	0 (0)	0 (0)

(numbers in parentheses are number on major diabetogenic drugs)

Constructing a series of four age related 2 by 2 contingency tables for diabetes or normal glucose tolerance versus diabetogenic drug use revealed that diabetic subjects were more likely to be on diabetogenic treatment (Mantel Haenszel  $\chi^2=5.859$ ,  $P=0.0155$ ; odds ratio=3.17, 95% CI 1.25-8.07).

Constructing a series of four age related 2 by 2 contingency tables for diabetes or IGT versus diabetogenic drug use revealed no difference between diabetic and IGT subjects regarding diabetogenic treatment (Mantel Haenszel  $\chi^2=0.899$ ,  $P=0.343$ ; odds ratio=2.99, 95% CI 0.31-28.8).

Similarly, there was no difference between normal and IGT subjects regarding diabetogenic treatment (Mantel Haenszel  $\chi^2=2.79$ ,  $P=0.095$ ; odds ratio=2.42, 95% CI 0.86-6.83).

Data were organised to allow comparison between the associations of diabetogenic treatment and antihypertensive treatment (Figure 5.18).

### Diabetes in the elderly.

Figure 5.18: diabetogenic and antihypertensive drug use in Melton in various subjects (numbers of subjects).

Subjects (number)	Anti-hypertensive	Diabetogenic
65-69 Diabetic (9)	6	3
65-69 IGT (12)	12	2
65 Normal (132)	17	10
70-74 Diabetic (4)	1	1
70-74 IGT (4)	0	0
70 Normal (55)	7	4
75-79 Diabetic (4)	1	1
75-79 IGT (2)	0	0
75 Normal (11)	5	6
80-85 Diabetic (7)	4	4
80-85 IGT (2)	1	1
80/85 Normal (23)	6	2
Diabetic versus normal		
Mantel Haenszel $\chi^2$ (P)	10.92 (0.0009)	9.58 (0.002)
Odds ratio (95% CI)	4.45 (1.8-10.8)	4.81 (1.8-13.0)

The data were put into a series of three 2 by 2 contingency tables for subjects aged 65 to 69, 70 to 79, and 80 to 85; Figure 5.18 also details the results of Mantel Haenszel tests examining whether normal versus diabetic subjects were taking similar numbers of anti-hypertensive and diabetogenic agents; both anti-hypertensive and diabetogenic medication were similarly associated with diabetes.

For each decade of diabetic subjects, the number of subjects taking anti-hypertensive or diabetogenic medication expected from the normal glucose tolerant subjects was calculated; again a series of three 2 by 2 tables was constructed of observed and expected antihypertensive use versus observed and expected diabetogenic drug use in the newly diagnosed diabetic subjects. The Mantel Haenszel  $\chi^2$  showed no significant difference in different types of drug use within diabetic subjects (Mantel Haenszel  $\chi^2=0.50$ ,  $P=0.48$ ; odds ratio 0.78, 95% CI 0.39-1.56).

IGT subjects did not differ from normal subjects regarding anti-hypertensive and diabetogenic drug use.

Thus it seems that both anti-hypertensive drug use and diabetogenic drug treatment are associated with the diagnosis of previously unrecognised diabetes in

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#### Newly found diabetic subjects.

Melton, to a similar degree; this is no great surprise, since the majority of subjects taking diabetogenic treatment were taking thiazide diuretics (indeed all of the newly diagnosed diabetic subjects on major diabetogenic drugs) and thiazides would also count as anti-hypertensive treatment. Unfortunately, I do not know the indications for the medications prescribed.

It has been shown in longitudinal studies in Gothenburg [312,313], that antihypertensive use is associated with the development of diabetes. Although these studies used only two main antihypertensive agents, thiazide diuretics and  $\beta$ -blockers, and there were no subjects with untreated hypertension, equal number of subjects developed diabetes or antihypertensive agent use first. In Rancho Bernardo, the survey of diabetes and hypertension categorising diabetes as known or unknown with or without fasting hyperglycaemia [313a] found that the prevalence of hypertension increased as the degree of diabetic glucose homeostasis worsened, and since 56-58% of hypertensive subjects were not taking antihypertensive medication, it was possible to see this effect whilst allowing for treatment. Thus again, as in the previous section (Section 5.18), it would seem that the diabetes and anti-hypertensive use are developing from some other cause rather than as a direct causal relationship.

Thus it is apparent that diabetes in the elderly, some features of hypertension and some treatment for hypertension are very closely intertwined and that the Melton survey is of insufficient size to unravel this problem. However, other studies show that this interrelationship has been developing for several decades, and insulin resistance may be a most important underlying factor [266].

## Diabetes in the elderly.

### 5.20: postural hypotension.

Postural hypotension was also sought by repeating the blood pressure readings with the subject standing upright for approximately 1 minute, and results are in Figure 5.19

Figure 5.19: postural hypotension versus glucose tolerance status (subjects with postural hypotension/subjects examined (numbers of subjects)).

Age	Diabetic subjects	IGT subjects	Normal subjects
65	1/9	2/12	21/132
70	0/4	0/4	4/45
75	1/4	0/2	0/11
>79	1/7	0/2	6/23

Many subjects had a systolic BP drop of 20mm Hg or more, but none were light headed on questioning.

There was no association between glucose tolerance status and postural hypotension (Mantel Haenszel  $\chi^2=0.494$ ,  $P=0.48$ ). It is interesting that in this apparently fairly fit group of elderly a postural drop in blood pressure is very common, for instance affecting 15.9% (95% CI 10.1-23.3) of the normal 65 year old subjects examined.

Figure 5.20: features associated with postural hypotension (numbers of subjects).

	Diabetic subjects	IGT subjects	Normal subjects
Sys-HT	0	1	10
Anti-HT	2	1	2
Either	2	1	10

Newly found diabetic subjects.

#### 5.21: intermittent claudication.

The subjects were asked for a history of intermittent claudication (IC) [235], and in all cases with a history of IC, the subjects had the appropriate absent foot pulses; 2 of the 4 normal subjects with a history of IC had had their symptoms since relieved by having femoral-popliteal arterial grafts, but I have included them in the analysis since I am looking at evidence of peripheral vascular disease rather than walking ability.

Figure 5.21: intermittent claudication and diabetes (numbers of subjects).

Subjects (number)	Number with IC
Diabetic (24)	2
IGT (20)	2
Normal (210)	4

Of the 8 with intermittent claudication, only 2, with normal glucose tolerance, had normal ECGs. Of the 2 diabetic subjects, 2 had angina; of the 2 IGT subjects, 1 had had a myocardial infarction and 1 had no symptoms of ischaemic heart disease: of the 4 normal subjects, 2 had angina, and 2 had no symptoms of ischaemic heart disease.

Comparing subjects with abnormal glucose tolerance to normal subjects, there was an association between diabetes/IGT combined and intermittent claudication (2 tailed Fisher's exact  $P=0.023$ ; odds ratio 5.89, 95% CI 1.04-32.78) but not for diabetic subjects (2 tailed Fisher's exact  $P=0.098$ ) or IGT subjects (2 tailed Fisher's exact  $P=0.07$ ) when these groups were considered individually.

Thus in Melton, any association between peripheral vascular disease (PVD) is very slight, using my method of defining PVD.

The Framingham study [314] found that femoral bruits and impalpable foot pulses were significantly more common in diabetic females of all ages, and diabetic males had an increased number of carotid bruits; the investigators did not report on intermittent claudication, so their study cannot be directly compared to the Melton study. However, this Framingham study did document a dramatic



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#### Diabetes in the elderly.

increase in cardiovascular and cerebrovascular morbidity in diabetic subjects with carotid bruits or impalpable foot pulses, which would remove them from the study population in the future. A different study from Framingham showed that the increased risk of vascular disease with diabetes was greatest for intermittent claudication with a risk of 4.16 to 4.99 compared to non-diabetic residents [315]

One further analysis from Framingham examined various vascular risk factors against the risk of sustaining various vascular events [316], and here diabetes and cigarette smoking both tended to favour developing PVD rather than ischaemic heart disease.

A study based on subjects drawn from GP population registers in Edinburgh [317] used Doppler measurements to derive the ankle brachial pressure index, and performed GTTs also; they found that IC was only weakly linked to diabetes on univariate ( $p < 0.1$ ) but not multivariate analysis, whilst the ankle brachial pressure index was more strongly linked (univariate  $P < 0.01$ ; multivariate  $P < 0.05$ ). Other factors such as smoking were far more significantly associated with PVD, and diabetes did not seem to determine whether the subjects developed ischaemic heart disease or PVD.

Thus there does appear to be an association between diabetes and PVD, but it is necessary to use large samples and/or very carefully search for the PVD and diabetes to show it.

It might seem odd that the association between PVD and diabetes is not easily demonstrated, since the diabetic subjects is 10 to 15 times more likely to have an amputation than a non-diabetic subject [35,318], but this is due to other factors such as neuropathy and poor wound healing interacting with the PVD to ensure that the diabetic heads off on the pathway to amputation [318].

Newly found diabetic subjects.

#### 5.22: symptoms and ECG evidence of ischaemic heart disease.

Subjects were questioned regarding a history of angina and previous myocardial infarctions (MI); angina was taken as per WHO standards [235], but a history of MI was taken as positive for either WHO standards or for having been told by a doctor that they had had one. Standard 12 lead electrocardiographs (ECGs) were taken, and coded by the Minnesota code [235]. This present section will examine the symptoms of ischaemic heart disease (IHD), angina and previous myocardial infarction, and ECG evidence of IHD, codable Q waves (codes 1-) and codable T wave inversion (codes 5-).

Figure 5.22: previous myocardial infarctions and angina in subjects (numbers of subjects).

Subjects (number)	Symptoms of IHD: Angina MI Either			ECG abnormality: Q T Either			Any
Male:							
65-69 Diabetic ( 7 )	3	3	4	2	2	3	4
65-69 IGT ( 9 )	0	2	2	2	2	3	3
65 Normal (62)	4	6	7	10	9	17	19
70-74 Diabetic ( 1 )	0	0	0	0	0	0	0
70-74 IGT ( 1 )	0	0	0	1	0	1	0
70 Normal (24)	2	4	5	10	5	14	14
75-79 Diabetic ( 3 )	0	1	1	0	2	2	2
75-79 IGT ( 1 )	0	0	0	0	0	0	0
75 Normal ( 5 )	0	1	1	0	0	0	1
80-85 Diabetic ( 3 )	0	1	1	1	1	1	1
80-85 IGT ( 0 )	0	0	0	0	0	0	0
80/85 Normal (10)	0	1	1	3	1	3	3
Female:							
65-69 Diabetic ( 2 )	0	0	0	0	0	0	0
65-69 IGT ( 3 )	0	0	0	0	0	0	0
65 Normal (70)	5	3	6	9	15	18	22
70-74 Diabetic ( 3 )	1	0	1	0	0	0	1
70-74 IGT ( 3 )	1	0	1	0	1	1	1
70 Normal (21)	1	0	1	1	2	3	4
75-79 Diabetic ( 1 )	0	0	0	0	0	0	0
75-79 IGT ( 1 )	0	0	0	0	1	1	1
75 Normal ( 6 )	0	0	0	0	0	0	0
80-85 Diabetic ( 4 )	1	1	1	1	2	2	2
80-85 IGT ( 2 )	0	0	0	0	0	0	0
80/85 Normal (13)	2	1	3	3	2	3	5

Note: Any=subjects with any symptom or ECG change of IHD.

Sexes were considered independently, and to obtain reasonable cell sizes, ages 65 to 74, and 75 to 85 were amalgamated, and a series of four 2 by 2 contingency

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tables constructed by glucose tolerance status and symptoms of IHD present for the ages and sexes concerned.

The Mantel Haenszel test revealed differences between diabetic and normal subjects regarding a history of angina (Mantel Haenszel  $\chi^2=5.32$ ,  $P=0.021$ ; odds ratio=4.56, 95% CI 1.26-16.79), and the presence of either of the two symptoms of ischaemic heart disease (Mantel Haenszel  $\chi^2=5.24$ ,  $P=0.022$ ; odds ratio=3.52, 95% CI 1.20-10.43), but there was no difference regarding a history of previous myocardial infarction (Mantel Haenszel  $\chi^2=3.52$ ,  $P=0.061$ ; odds ratio=3.57, 95% CI 0.95-13.50). The significant differences between the groups of diabetic and normal subjects were due to the differences within male subjects ( $P<0.025$ ), rather than female subjects ( $P>0.05$ ).

There was no difference using the Mantel Haenszel test between IGT and normal subjects ( $P>0.1$ ) regarding symptoms of IHD.

Similarly, a series of four 2 by 2 contingency tables was constructed for each sex and amalgamated age group by glucose tolerance status and by ECG abnormality. A Mantel Haenszel  $\chi^2$  test revealed no difference between diabetic and normal subject regarding presence of Q waves, presence of T inversion, presence of either of these abnormalities or presence of any symptom or ECG sign of IHD ( $P>0.1$ ; lower 95% CL<0.7). Similarly, there was no significant difference between normal and diabetic subjects when examining just male or just female subjects ( $P>0.05$ ).

There was no difference using the Mantel Haenszel test between IGT and normal subjects ( $P>0.3$ ) regarding ECG changes of IHD.

Normal glucose tolerant subjects were also examined to see if there was any sex difference for the above features in a series of two 2 by 2 contingency tables.

There was a sex difference regarding history of previous MI (Mantel Haenszel  $\chi^2=4.00$ ,  $P=0.045$ ; odds ratio=3.61, 95% CI 1.03-12.69); otherwise angina, codable Q waves, codable T wave inversion or combinations of these revealed no sex difference within normal subjects ( $P>0.08$ ; lower 95% CL<1.0).

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#### Newly found diabetic subjects.

Amalgamating diabetic and IGT subjects, and then comparing them to normal subjects as above for symptoms and ECG signs of IHD revealed no difference using a Mantel Haenszel test ( $P > 0.1$ ; odds ratio lower 95% CL  $< 0.75$ )

Thus the Melton study suggests that even at this early stage of their diabetes, angina is associated with diabetes and a history of an MI weakly associated ( $P = 0.061$ ). The Nottingham study comparing 98 elderly diabetics to non-diabetic controls [40] showed no association between diabetes and angina, and borderline association with myocardial infarction and heart failure ( $0.1 > P > 0.05$ ). A Dutch study of late complications again revealed no association between diabetes and history or ECG evidence of IHD [232]. One study did show an association between diabetes and both coronary artery disease and previous myocardial infarction in older subjects [229]; however, the investigators do not specify how they defined coronary artery disease, and more significantly, the patients were selected from hospital diabetic clinics and are likely to be biased towards diabetic subjects with other problems.

The Zutphen study screened 400 men [319] with a 50 g GTT and classified results of area under the GTT curve by quartiles; here the highest quartile was significantly more likely to develop IHD than the lower quartile, but this did not apply to other forms of vascular disease or for diabetic versus non-diabetic subjects.

In the Whitehall study, newly found diabetic subjects were significantly more likely than normal subjects to have ST depression, left bundle branch block and sinus tachycardia [320].

Thus neither Melton or Whitehall studies had strong evidence of myocardial infarctions on the history or ECG of the subject, although there is undoubtedly an association between diabetes and ischaemic heart disease, which may not be not dependent on disease duration [265]. It may well be that subjects with diabetes who sustained an MI were investigated leading to the discovery of their diabetes, so that they were in the known diabetic groups in these studies; also it may be that, due to their significantly increased mortality after an MI compared to normal

### Diabetes in the elderly.

subjects [321-323], that there were fewer diabetic subjects with a previous history of an MI surviving.

#### 5.23: electrocardiographic abnormalities: LVH/RVH.

The ECGs were examined for evidence of left ventricular hypertrophy (LVH; Minnesota codes 3-1, 3-3, 3-4) and right ventricular hypertrophy (RVH; Minnesota code 3-2) [235], and results documented in Figure 5.23.

Figure 5.23: ventricular hypertrophy and glucose tolerance status.

	Number	LVH	RVH
Diabetic			
M	14 ( 8)	1 (1)	0 (0)
F	10 ( 5)	1 (0)	0 (0)
IGT			
M	11 (10)	0 (0)	0 (0)
F	9 ( 6)	1 (1)	0 (0)
Normal			
M	100 (85)	2 (2)	0 (0)
F	110 (910)	5 (3)	0 (0)

Numbers in parentheses are subjects aged 65 to 74.

Whichever way the data were analysed, there was no association between any ventricular hypertrophy and abnormalities of glucose tolerance (2 tailed Fisher's exact  $P > 0.05$ ). Unfortunately the Whitehall study did only a 6 lead ECG [318], and thus they would not detect all cases of ventricular hypertrophy.

#### 5.24: electrocardiographic abnormalities: bundle branch blocks.

Again the ECGs were examined; under left bundle branch block (LBBB; Minnesota code 7-1-1), I also included partial LBBB (Minnesota code 7-6), and left anterior hemiblock (Minnesota code 7-7) [235].

Under right bundle branch block (RBBB; Minnesota code 7-2-1), I also included partial RBBB (Minnesota code 7-3) and RSR' in  $V_1$  or  $V_2$  (Minnesota code 7-5).

Intraventricular conduction defects (IVB; Minnesota code 7-4) and first degree block (Minnesota code 6-3) were also noted.

#### Newly found diabetic subjects.

No subjects had second or third degree block, or left posterior hemiblock.

The results are in Figure 5.24.

Again, whichever way one examined the data, there were no associations between any conduction defect and diabetes (2 tailed Fisher's exact  $P > 0.05$ ). If the diabetics were going to have a ventricular conduction defect, they had RBBB, but this trend compared to the normal glucose tolerant group is still not significant (2 tailed Fisher's exact  $P = 0.214$ ).

Figure 5.24: cardiac conduction defects and glucose tolerance status (numbers of subjects).

	Number	LBBB	RBBB	IVB	1°	any
Diabetic						
M	14	0	1	0	1	2
F	10	0	2	0	0	2
IGT						
M	11	1	0	0	0	1
F	9	0	0	0	0	0
Normal						
M	100	6	4	1	5	16
F	110	3	4	1	1	9

The Whitehall study showed that newly diagnosed diabetic subjects had excess LBBB [320], and a study in known diabetic subjects compared to treated hypertensive subjects [324] revealed excess RBBB and first degree block. I am unable to confirm these findings.

#### 5.25: electrocardiographic abnormalities: arrhythmias.

The ECGs were also examined for any arrhythmias such as atrial premature beats (Minnesota code 8-1-1), ventricular premature beats (Minnesota code 8-1-2), parasystole (Minnesota code 8-2-4), persistent atrial fibrillation (Minnesota code 8-3-1), sinus tachycardia (Minnesota code 8-7), and sinus bradycardia (Minnesota code 8-8) [235]. Results are given in Figure 5.25.

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Figure 5.25: arrhythmias and glucose tolerance status (numbers of subjects).

	ECG codes for arrhythmias:						
	Number	8-1-1	8-1-2	8-2-4	8-3-1	8-7	8-8
Diabetic							
M	14	0	0	0	1	0	0
F	10	0	1	0	1	0	0
IGT							
M	11	1	0	0	0	1	0
F	9	0	0	0	0	0	0
Normal							
M	100	1	5	0	2	1	2
F	110	2	0	1	2	0	0

There was no association whatsoever between any arrhythmia, or all combined, and glucose tolerance status (2 tailed Fisher's exact  $P > 0.05$ ).

The Whitehall survey found increased sinus tachycardia in newly diagnosed diabetic subjects [320], but the other arrhythmias were no different from those in normal subjects, and were not mentioned as differing between diabetic and hypertensive individuals in the Leicester clinic study [324].

### 5.26: any electrocardiographic abnormalities.

Finally one can consider whether the diabetic was more likely to have any abnormality of the ECG present (Figure 5.26).

Figure 5.26: any ECG abnormality versus glucose tolerance status (number of subjects).

	Number	Any ECG code
Diabetic		
M	14	8
F	10	10
IGT		
M	11	8
F	9	2
Normal		
M	100	49
F	110	32

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#### Newly found diabetic subjects.

In normal glucose tolerant subjects, males were far more likely to have an abnormal ECG than females (2 tailed Fisher's exact  $P=0.0044$ ; odds ratio 2.32, 95% CI 1.28-4.31), and this applied to a less degree in IGT individuals (2 tailed Fisher's exact  $P=0.023$ ); this sex differential did not apply in diabetic subjects (2 tailed Fisher's exact  $P=0.68$ ), suggesting that diabetes may remove the protection from IHD of the female sex, or the study sample was too small to show the sex differential.

Otherwise, there were no associations between different categories of glucose tolerance and overall presence of any ECG abnormalities.

#### 5.27: conclusions.

This study has been hampered by the surprisingly small number of subjects found with previously undiagnosed diabetes, and the poor selection of control subjects which are skewed towards the younger age groups. Also, subjects with known diabetes were not examined, so that the conclusions apply to only those previously undiagnosed diabetic subjects.

Nonetheless, it is apparent that in these elderly diabetic subjects, very few have diabetic symptoms, particularly if aged over 78; there is no association between presence of symptoms and presence of glycosuria.

The newly diagnosed diabetic subjects did not have an increased body mass index, but in the subjects aged 65-74 years 77% were shorter than the normal subjects' median height, suggesting that diabetic subjects might be shorter (1 tailed Fisher's exact  $P=0.054$ ).

As well as obesity, positive family history and a history of heavy babies were also not more common in the diabetic group; it may well be that diabetic subjects with these features have already been identified because of these features.

However, even at this early stage in the course of their diabetes, the diabetic subjects had evidence of both specific and non-specific complications. 1 subject had background retinopathy, and evidence of neuropathy (decreased ankle tendon



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### Diabetes in the elderly.

reflexes) was more common in diabetic than normal subjects (odds ratio 4.4, 95% CI 1.5-27.5).

There was evidence of increased risk of non-specific complications in the diabetic subjects compared to normal subjects, such as cataracts (odds ratio 4.7, 95% CI 1.6-14.2), and carpal tunnel syndromes (odds ratio 9.7, 95% CI 1.5-66.7).

Most interesting were the associations with vascular risk and disease; considering any abnormality of glucose tolerance versus normal subjects, there was increased risk of previous stroke (odds ratio 5.9, 95% CI 1.3-27.5), and intermittent claudication (odds ratio 5.9, 95% CI 1.0-32.8). Comparing diabetic to normal subjects, they had increased risk of retinal artery occlusion (odds ratio 68.5, 95% CI 4.2-301.0), history of angina (odds ratio 4.6, 95% CI 1.3-16.8), any evidence of hypertension combined (LVH, systolic hypertension or antihypertensive use) (odds ratio 5.2, 95% CI 1.6-16.6), and use of antihypertensive agents (odds ratio 4.5, 95% CI 1.8-10.8): diabetogenic drug treatment was really just as likely to be associated with diabetes as antihypertensive agent use (odds ratio 4.8, 95% CI 1.8-13.0), which is probably due to thiazide diuretics being a common agent in both classes of treatment. It may well be that insulin resistance underlies the close inter-relationship between diabetes, hypertension and vascular disease.

Thus at this early stage both specific and non-specific complications are present. It is unlikely that elderly subjects will refer themselves to the GP with absent ankle reflexes, but the link to vascular disease is marked; thus subjects with vascular disease should be considered for diabetes testing, and should have at least a random blood glucose estimation.

Since the retinopathy and neuropathy were occurring in subjects in their 60s and 70s as well as at older ages, their diabetes must have developed at a younger age, and this would require screening at this younger age to detect it prior to the development of specific complications.

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## Mortality in diabetic subjects.

### Chapter 6: mortality in diabetic subjects.

#### 6.1: introduction.

It was generally accepted in textbooks and review articles that the impact of diabetes on mortality in the elderly was minimal with life expectancy similar for diabetic and non-diabetic subjects [43,105,325,326] after the age of 70 to 75 years; this was presumably due to the shorter life expectancy in all elderly subjects with other competing causes of death minimising the effect of diabetes, or any one particular illness. Some authors confirmed that the excess mortality associated with diabetes did decline with age, particularly after 65 years, but found that this excess was still present until the age of 80 years [327]. One could also be distracted by the mortality in younger diabetic subjects which is greatly increased as demonstrated in Figure 6.1 [123].

Figure 6.1: years of life remaining in Joslin clinic diabetic patients compared to non-diabetic subjects at different ages [123].

Age (years)	Remaining years of life:	
	Diabetic	Non-diabetic
10	44.3	61.5
20	36.1	51.9
30	30.1	42.5
40	23.7	33.3
50	16.9	24.7
60	11.3	17.2
70	7.2	10.9

Previous studies have examined the mortality in diabetic subjects recruited from diabetic clinics, local populations of known diabetic subjects, and populations screened for diabetes.

In two mammoth, long term, follow up studies, the diabetic patients attending the Mayo clinic were followed up from 1939 and the results analysed by two different authors. Kessler [328] showed that diabetic men had excess mortality until aged 80 and diabetic women had excess mortality until aged 85. Hirohata *et al* [329] found that diabetes was associated with increased mortality at all ages in both sexes except in males aged 60 to 79 years with diabetes of less than 5 years

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### Diabetes in the elderly.

duration. To illustrate the difficulties of mortality studies, these studies, using the same source of diabetic subjects, disagreed as to whether diabetes was [328] or was not [329] associated with excess mortality in diabetic subjects aged less than 19 years over the first 15 years of their diabetes. Hirohata *et al* reported relative survival rather than mortality and since the different cohorts of their reference normal population had different mortality rates, it is not possible to calculate the mortality ratio for the combined cohorts. However Hirohata's data show that in each age group, survival is less with increasing duration of diabetes [329]. Kessler [328] does give data enabling calculation of age specific relative mortality (Figure 6.2); he also shows that the actual number of deaths expected were low in subjects aged 60 and over in 1939, and steadily increased until plateauing in 1951-1955 as the elderly population accrued. Thus data from the past may not be appropriate to the population of today, since there were so few elderly, although for all ages from 1931 to 1959, the mortality ratio only varied between 1.40 to 1.74 with no trend [328].

In Birmingham, diabetic clinic patients presenting from 1960 to 1968 were followed until 1975 [330]; even at ages greater than 80, there was a slight excess of male deaths (mortality rate 112%) and a greater excess of female deaths (mortality rate 133%) (Figure 6.2).

All the above studies were likely to include IGT subjects as diabetic since they were based on subjects diagnosed as diabetic prior to 1979 (see Section 2.3). Since subjects with IGT have an intermediate mortality between that of diabetic and normal subjects [44], their inclusion in the diabetic group would decrease the apparent effect of diabetes on the subjects' mortality minimising the full effect of diabetes.

There have been two recent studies in Scotland examining mortality in clinic populations who were unlikely to have included IGT subjects. Waugh in Dundee [331] examined subjects attending a diabetic clinic which included all IDDM subjects, but overall 33% of NIDDM subjects were attending their GP instead; the elderly, in particular, were more likely to be under GP care. He found an

### Mortality in diabetic subjects.

increased risk of death at ages greater than 75 years (Figure 6.3). Waugh also found that diabetes mellitus was documented on the death certificate in only 70% of cases.

Figures 6.2: Mortality ratios (%) for different diabetic groups at different ages relative to non-diabetic population.

Age (years)	Diabetic population:							
	GDR[335] Both Sex	Joslin [328] Male	Joslin [328] Female	Edinburgh[336] Male Female		Birmingham [330] Male Female		
0- 9	315	43	214					
10-19	408	375	714					
20-29	517	629	870					
30-39				497	847	357	167	
40-49	532	548	676					
50-59	379	249	300	244	455	160	200	
60-69	228	181	262	239	281	136	300	
70-79	195	163	244	165	303	126	200	
80+		150	202	135	198	124	153	
70+	137							
80+		118	145	101	116	112	133	

Figures 6.3: Mortality ratios (%) for different diabetic groups at different ages relative to non-diabetic population.

Age (years)	Diabetic population:			
	BDA [338] Male	BDA [338] Female	Tayside [331] Both Sexes	Aberdeen [332] Both Sexes
15-44	306	525	550	256
45-64	198	272	230	298
65-74			170	162
65+	138	197		
75+			130	88

Wong [332] examined subjects attending one clinic and assumed that this included all the diabetic subjects in that area; the reason for this implausible belief

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### Diabetes in the elderly.

was that 96% of NIDDM subjects from a group of keen general practices were attending the clinic, but the proportion from other general practices is not given. Interestingly Wong found that diabetes was associated with less risk of death in subjects aged greater than 75 (Figure 6.3); the finding that a disease improves survival in the Western world is biologically implausible and highly likely to reflect a bias in the subject selection.

So overall, studies based on clinic patients tend to show increased mortality at all ages. However, these results may not apply to all diabetic subjects. Ignoring differences due to time and location of study, there are two other factors which may well bias the results. Firstly, for whatever reason, clinic attendance may well improve survival as demonstrated by Hayes *et al* in Cardiff [181] (see Section 4.1). Secondly, one has to consider the type of patient in the clinic. It may well be that general practitioners refer the elderly diabetic patients only if they have developed problems, which would increase the mortality of a clinic population. On the other hand, a sick elderly patient could have their diabetes forgotten amongst all their other medical, social and psychiatric problems, which would tend to elevate the death figure in the non-diabetic group. If the diabetes was not forgotten, the general practitioner might still not refer the patient to the diabetic clinic believing that the clinic had nothing to offer the patient, or might refer the patient to a medical or geriatric clinic instead. Finally, many diabetologists would follow up elderly diabetic subjects (see Chapter 7); this would include diabetic patients presenting as general medical emergencies who would be likely to have a decreased survival. Thus clinic attendance may well improve survival, but the direction of bias introduced by subject selection for clinic attendance is uncertain. Several studies examined the mortality rate in community based studies of known diabetic subjects.

Bale and colleagues [333] used data from the NHIS III study in the USA to estimate the number of diabetic subjects in Iowa and collected death certificates to identify diabetic subjects who had died rather than to ascertain that a subject already known to be diabetic had died; since death certificates in Iowa list all

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#### Mortality in diabetic subjects.

morbid conditions, it was hoped that the number of diabetic subjects dying would be accurately ascertained. Pennsylvania has a similar comprehensive death certificate and diabetes there is under-reported by 7.6% [333]. Bale found that survival was the same for diabetic and non-diabetic people at age 65 onwards for both sexes.

Panzram followed up subjects registered with the GDR diabetes register in Erfurt [334]; if you don't get registered, you don't get treated so it is assumed that this is a very comprehensive register; as in Section 2.1, the elderly, diet treated, diabetic person may not use any prescribed items and be omitted from this register. Here 10 year follow up revealed that there were no excess deaths in diabetic subjects aged 75 or more. Interestingly, Panzram demonstrated a significant increased mortality after just one year of diabetes which he attributed to vascular disease developing during a long period before the NIDDM was found; other contributory factors to this early increase in mortality would be that those NIDDM subjects who developed vascular disease were diagnosed but those that did not develop complications would remain undiagnosed, and it may well be that the features of Reaven's syndrome X [266] of insulin resistance, NIDDM, dyslipidaemias, hypertension and vascular disease develop concomitantly.

However, a similar study by Michaelis [335] using ambiguous diagnostic criteria, "1965 and 1980 WHO criteria", and the whole GDR population from 1961 to 1987, found that there was an excess mortality at all ages (Figure 6.2).

Shenfield followed up subjects found on a survey of known diabetic subjects in Edinburgh [336] and again showed an increased mortality in all age groups except males aged 85 or more (Figure 6.2).

Hodkinson *et al* [337] followed up a group of elderly subjects aged 65 or more picked from several towns in the UK; it was found that known diabetes at the time of the original survey was associated with increased subsequent mortality in women but not men.

Fuller *et al* [338] followed up British Diabetic Association (BDA) members and found that in subjects aged 65 or more, both sexes had an increased mortality

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### Diabetes in the elderly.

ratio, although the results for smaller cohorts of older subjects are not given. It was also found that diabetes appeared on only 67% of the death certificates.

There have been several studies examining large populations of known diabetic subjects such as the NHANES I in the USA and the Framingham and Rochester studies [339-342], but unfortunately these did not report age specific prevalences, or merely reported the plain death rate in the diabetic subjects [342].

One previous study in Melton examined survival in subjects aged 75 or more; here hypoglycaemic drug use was associated with a 3.30 to 3.34 relative risk of death over 5 years, and one presumes that this was due to the diabetes rather than the treatment [154].

All these population studies cover known diabetic subjects with the consequent problem of an incomplete picture due to under-ascertainment of the full size of the diabetic population, and the inclusion of subjects with undiagnosed IGT and diabetes in the normal group. Since the Bedford survey showed an increased mortality in newly diagnosed diabetic and IGT subjects [44], their inclusion in the normal group would artificially increase its mortality, thus minimising the apparent effect of diabetes on survival.

Several populations have been screened for diabetes and followed up, but these surveys often concentrated on subjects younger than 65 years [259,260,343], and other surveys again do not give age specific rates [344]. After the Bedford screening survey, it was found that there were more deaths in the diabetic subjects compared to subjects with IGT and normal glucose tolerance [44]; known diabetic subjects were not included in this study, and although it was noted that the subjects who died tended to be older than the survivors, age specific rates were not given; however, I suspect that the Bedford study was the basis for the conclusions in a geriatric metabolic textbook to which I referred earlier [327], showing an increased mortality until the age of 80. Kaltiala and colleagues in Tampere [345] followed up octogenarian subjects known to be diabetic and those with fasting hyperglycaemia in comparison to subjects without fasting hyperglycaemia, which is not the same as diabetic versus normal glucose tolerance (see Sections 2.3, 4.3);

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#### Mortality in diabetic subjects.

it was found that known diabetic subjects had an increased risk of death over 5 years but those with fasting hyperglycaemia had no appreciable increase in mortality.

Stengård *et al* [346] followed up subjects from the East and West Finland study [26], and found an increased risk of death in elderly men with diabetes, but not with IGT. However, as previously discussed (Section 2.5), the study may have overestimated the number of diabetic subjects by a short period of fasting and by performing some GTTs in the afternoon, and the prevalence obtained was double that obtained in another Finnish study [25]; thus subjects with diabetes may have been diluted with IGT subjects, reducing the full effect of the diabetes on survival.

Maltese subjects were screened by GTT [346a], and on 4 year follow up, allowing for sex and age, diabetic subjects aged 60 years or more had an odds ratio of 1.77 (95% CI 1.11-2.38) of death compared to normal glucose tolerant subjects; however the age structure of this elderly group is not given.

The most relevant study is that of Agner *et al* who performed GTTs in subjects aged 70 and followed them up for 10 years [23]; they found that the diabetic men were 1.47 times more likely to die than normal glucose tolerant subjects and this ratio in females was 2.71. However, this reported the difference in number of deaths over a 10 year period, and this long time period may have obscured the association of diabetes with premature death, since if one waits long enough, the proportion dead in each study group will be the same, 100%. This effect can be overcome by comparing the actual survival curves using Cox's proportional hazards model [347], rather than the numbers alive at one particular time.

Thus there are several problems on studying the effect of diabetes on mortality.

I have already mentioned bias introduced on examining clinic populations, underascertainment of the full impact of diabetes by considering only known diabetic subjects, confusion introduced by including subjects one would now classify as IGT in the diabetic group, and long periods of follow up minimising any premature mortality. There are still more problems.



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### Diabetes in the elderly.

Firstly some studies use death certificates to ascertain how many deaths occur in diabetic subjects [333,338,348], rather than to just ascertain that a subject has died; however, death certificates are notoriously unreliable regarding the actual recording of diabetes; only 33 to 38% of deaths in diabetic subjects have diabetes mentioned on the certificate on studies from the USA [341,342]; the corresponding UK figures are 67 to 70% [331,338].

Secondly, maximum subject inclusion in follow up studies is vitally important, since it is not surprising to learn that those lost to follow up are actually dead [349]; the last 10.6% "hard to trace" American retirees when finally tracked down by intensive tracing raised the death rate by 15.5%.

Thirdly, there is great variation in what is reported. The majority of studies report relative mortality or give data allowing its calculation [23,44,328,330-332,334,335,336,345], but some report relative survival [329], some just a plain death rate with no comparison to a normal population [342], some just years of life left [123,333], some a plain cumulative mortality [344], and some merely give the significance levels attained [337]. The majority of studies report on age at death [328,330-332,335,336], but some report on age at diagnosis of diabetes [44,329,334,342], some on age at start of study period [23,333,345], or on duration of diabetes [339]. Different studies use different age strata for age specific rates (Figures 6.2, 6.3), and some studies do not give age specific rates.

All these factors make understanding the full impact of diabetes on survival difficult. Most studies suggest that mortality is increased in diabetic subjects to a late age, but one wonders if the full effect of diabetes on mortality is under-estimated; this was examined as part of the Melton diabetic survey.

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### Mortality in diabetic subjects.

#### 6.2: method.

The diabetic survey was performed as described in Chapter 2; the subjects were also registered with the Office of Population Censuses and Surveys (OPCS) to collect death certification details whenever and wherever the patient died in the UK. Death certificates were used to ascertain that the patient had died, the cause of death, and whether diabetes was recorded on the certificates of dead diabetic subjects.

The death certificates were collected for the 4½ years from the start of the diabetic survey; this took several months longer than the 4½ years to allow for the delay in OPCS processing the death certificates.

Unfortunately the survey took approximately 12 months to complete; subjects tested towards the end of the survey had already lived one year (and through one winter) longer than subjects tested at the start of the survey, and thus might have been selected as survivors; this would not have had a great effect on comparison within subjects tested since the diabetic subjects were found evenly spaced throughout the year, but the known diabetic subjects might have been culled during the winter, and therefore comparing the known diabetic subjects to those tested later on would have overestimated the effect of known diabetes on mortality. One way to tackle this problem would be to start looking for survival after the end of the study among only those subjects alive at that time; however, this would have missed many deaths, and given less subjects to observe. Therefore a Cox's proportional hazards model was used to compare mortality between the different groups taking into account the subjects' sex, age and date of testing.

Census date was taken as 1/8/87 for subjects whose glucose tolerance status was already known, ie known diabetic subjects and 3 subjects who had had recent glucose tolerance tests. For other subjects, census date was taken as the date on which the GTT was either performed or refused.

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### Diabetes in the elderly.

#### **6.3: Results: survival and mortality.**

The number of each group of subjects classified by age, sex, and glucose tolerance status alive at various times is shown in Figure 6.4.

The first death in the newly diagnosed diabetic group occurred 13 months after testing, and in the known diabetic group the first death occurred 5 months after diagnosis. Since the GTTs were done in subjects with no acute illnesses, it seems likely that the diabetic GTT results were due to diabetes rather than the stress of an illness, and the mortality rates apply to a diabetic group rather than an ill group who also had stress related hyperglycaemia.

Mortality in diabetic subjects.

Figure 6.4: life table of survival in Melton.

Subject	Number of subjects alive:					
	8/87	8/88	8/89	8/90	8/91	3/92
<b>65 male:</b>						
Known DM	3	3	3	2	2	2
New DM	5	5	5	5	2	2
IGT	9	9	9	9	9	9
Normal	86	86	85	83	83	80
<b>65 female:</b>						
Known DM	6	5	5	4	4	4
New DM	2	2	2	2	1	1
IGT	5	5	5	4	4	3
Normal	112	111	109	105	105	105
<b>70 male:</b>						
Known DM	7	5	4	4	3	3
New DM	0	0	0	0	0	0
IGT	3	3	2	2	2	2
Normal	59	59	59	57	56	54
<b>70 female:</b>						
Known DM	10	9	9	8	8	7
New DM	3	3	3	3	3	3
IGT	4	4	4	4	4	4
Normal	65	65	64	63	62	62
<b>75 male:</b>						
Known DM	8	7	5	3	3	2
New DM	1	1	1	1	1	1
IGT	7	7	6	6	6	6
Normal	42	42	40	40	37	36
<b>75 female:</b>						
Known DM	9	8	7	6	4	4
New DM	1	1	1	1	1	1
IGT	5	5	5	5	5	5
Normal	76	76	73	72	71	70
<b>80 male:</b>						
Known DM	4	3	3	1	1	1
New DM	3	3	3	2	1	1
IGT	5	5	5	4	3	3
Normal	23	23	22	20	19	18
<b>80 female:</b>						
Known DM	2	1	1	1	1	1
New DM	1	1	1	1	1	1
IGT	0	0	0	0	0	0
Normal	34	34	31	29	26	26
<b>85 male:</b>						
Known DM	2	2	1	0	0	0
New DM	0	0	0	0	0	0
IGT	2	1	0	0	0	0
Normal	5	5	5	4	4	4
<b>85 female:</b>						
Known DM	1	1	1	1	1	1
New DM	3	3	2	2	2	2
IGT	4	4	4	3	3	3
Normal	18	18	15	11	9	9

## Diabetes in the elderly.

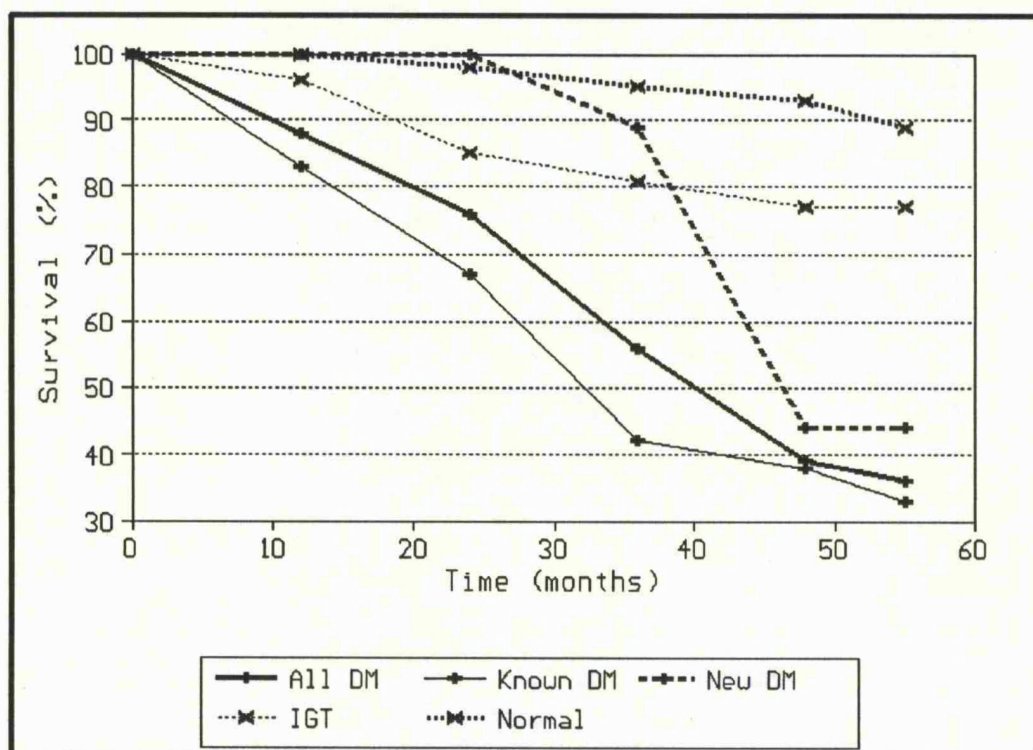
Figure 6.4 continued: life table of survival in Melton.

Subject	Number of subjects alive:					
	8/87	8/88	8/89	8/90	8/91	3/92
<b>All male:</b>						
All DM	33	28	24	17	12	11
Known DM	24	20	16	10	9	8
New DM	9	9	9	8	4	4
IGT	26	25	22	21	20	20
Normal	215	215	211	204	199	192
<b>All female:</b>						
All DM	38	34	32	29	26	25
Known DM	28	24	23	20	18	17
New DM	10	10	9	9	8	8
IGT	18	18	18	16	16	15
Normal	305	304	292	279	272	271
<b>Both sexes:</b>						
All DM	71	62	57	46	38	36
Known DM	52	44	39	30	27	25
New DM	19	19	18	17	12	12
IGT	44	43	40	37	36	35
Normal	520	519	503	483	471	463

DM=diabetic subjects; IGT=impaired glucose tolerant subjects

These data are expressed graphically in Figures 6.5-6.7.

Figure 6.5: survival of male subjects in Melton.



# Mortality in diabetic subjects.

Figure 6.6: survival of female subjects in Melton.

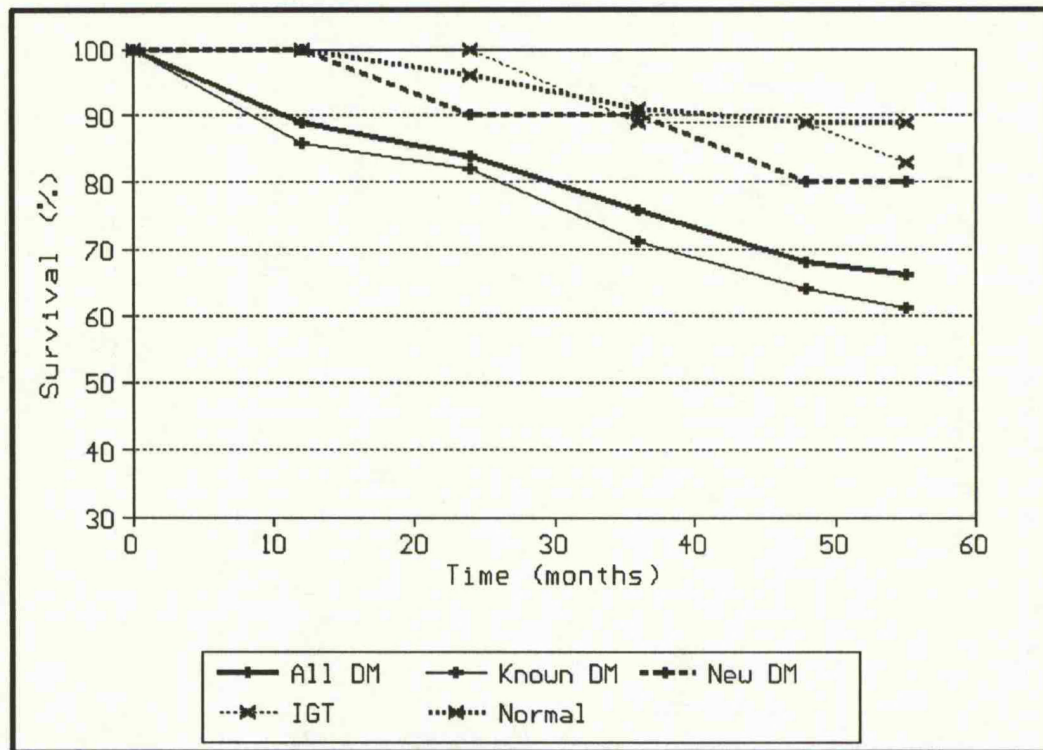
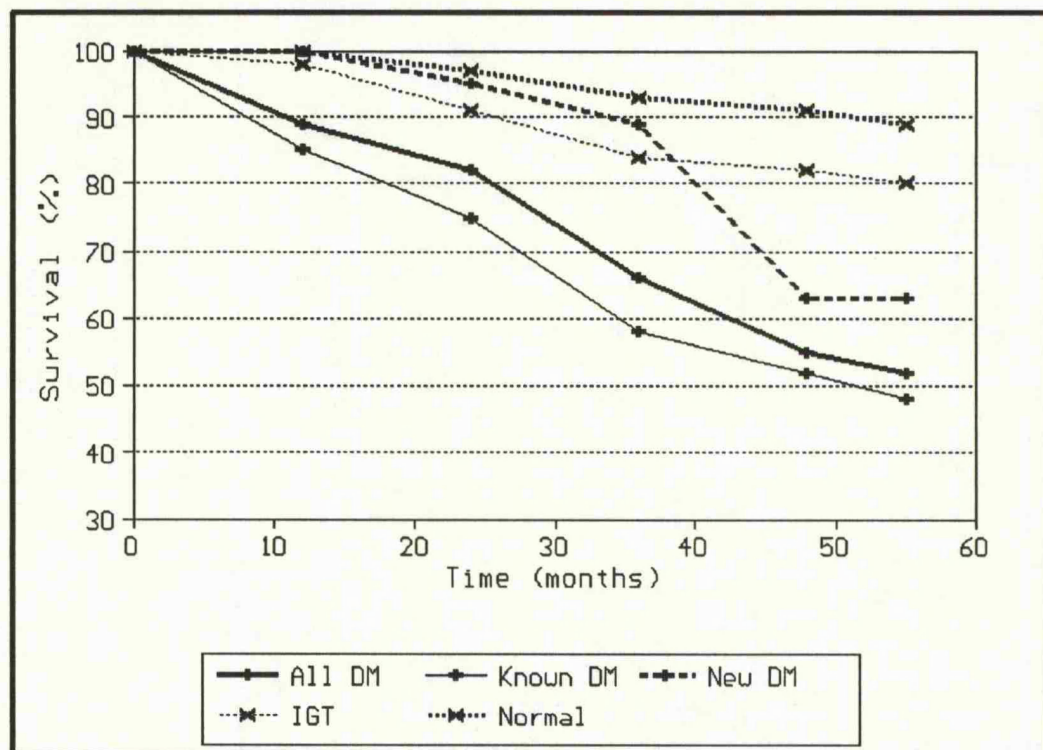


Figure 6.7: survival of subjects of both sexes in Melton.



### Diabetes in the elderly.

If the survival curves follow a straight line, then 50% of diabetic subjects are dead in 55.6 months compared to 50% of normal subjects in 236.6 months.

The data were analysed by the Cox's model to compare mortality of subjects with different categories of glucose intolerance to mortality of subjects with normal glucose tolerance of all ages allowing for age, sex and sampling time (see Figure 6.8); the results were also analysed to compare mortality of all diabetic subjects (ie known and new) to normal subjects for each age group (see Figure 6.9).

Figure 6.8: results of Cox's proportional hazards model comparing subjects' mortality to mortality with normal GTT.

Subject	Relative risk (95%CI)	
Known DM	5.2	(3.2-8.5)
New DM	3.0	(1.3-6.6)
All DM	4.5	(2.9-7.0)
IGT	1.7	(0.8-3.5)
Refused	1.5	(1.001-2.4)

Figure 6.9: results of Cox's proportional hazards model comparing age specific diabetic subjects' mortality to mortality with normal GTT.

Age	Relative risk (95%CI)	
65	12.12	(3.51-41.81)
70	4.74	(1.37-16.36)
75	6.96	(2.99-16.21)
80	2.48	(0.78-7.86)
85	1.34	(0.37-4.93)

Comparing previously diagnosed diabetic subjects to newly diagnosed subjects revealed that those with previous diabetes were more likely to die with a relative risk of 1.8 (95% CI 1.2-2.6); this is not surprising since it has previously been shown that greater duration of disease is associated with a greater mortality at each age [329].

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#### Mortality in diabetic subjects.

The mortality was compared between those that refused the GTT and those that accepted (new diabetic subjects, IGT subjects, and normal subjects combined) using the Cox's model and there was no difference in mortality between these two groups ( $P=0.75$ ). This difference in survival between participants and non-participants was also examined in Section 3.7 using a  $\chi^2$  test on the number surviving, and again no difference was found.

There was no sex difference in number of deaths over 4½ years of normal subjects either within each age group (2 tailed Fisher's exact  $P>0.1$ ), or over all age groups (Mantel Haenszel  $\chi^2=0.51$ ,  $P=0.47$ ; odds ratio=0.48, 95% CI 0.53-1.34).

Thus these results show a far higher increase in risk of death in diabetic subjects than previously reported and a relative risk of death for all elderly diabetic subjects of 4.5 times is truly dramatic (Figures 6.8). Furthermore, this risk was elevated at all ages (Figure 6.9), although in octogenarians the lower 95% confidence intervals do fall below 1.0. This dramatic increase found in Melton compared to other studies probably relates to full ascertainment of the study population with diabetic subjects being compared to normal glucose tolerant subjects whereas other studies would have compared known diabetic subjects to a group of subjects with normal, impaired and diabetic glucose tolerance. The lower 95% confidence interval of relative risk of death in this Melton study does overlap the known diabetic relative risk in a previous Melton study [154], and the relative risk of newly diagnosed diabetic subjects in Finland [346]; this is further confirmatory evidence of the dramatic risk of death associated with diabetes in the elderly.

The confidence intervals are wide due to the small number of deaths in some subsets, and apparently confidence limits of odds ratios increase exponentially; hopefully, given time and more deaths, the figures will become more precise with tighter confidence intervals.



#### Diabetes in the elderly.

##### 6.4: presence of diabetes on death certificates.

It had previously been documented that recording of diabetes on the death certificate of diabetic subjects is low [331,338,341,342]; Figure 6.10 shows the recording on Melton diabetic subjects. There is no difference in recording between known diabetic subjects and subjects found to be diabetic during the Melton survey (2 tailed Fisher's exact  $P=0.67$ ). One previous study [344] from Oxford, Massachusetts found that 22 of 35 deaths in known diabetic subjects had diabetes recorded on their death certificate, but only 11 of 34 newly diagnosed diabetics had diabetes recorded on their death certificate, which is a significant difference (2 tailed Fisher's exact  $P=0.016$ ). This difference which did not exist in the Melton study might have been because I was in the Melton general practice frequently, reminding the general practitioners about diabetes; however, the Oxford study had a slightly higher overall reporting rate of diabetes at 49%, and it is more likely that the reporting of known diabetes on the certificates was low in Melton.

As in previous reports, this is a low rate of recording (41%, 95% CI 25-59%), and is lower than the 67 to 70% in the other UK studies [331,338]. This low rate might be because the certifying doctor did not consider that the diabetes contributed to the death rather than merely forgetting about the diabetes; this is a deficiency of the UK death certificate which requests only the immediate cause of death, unlike certificates in Ohio and Pennsylvania where all morbid conditions are listed [333]

Figure 6.10: recording of diabetes on death certificate by group of diabetic subject (numbers of subjects).

	Diabetes on certificate:	
	Yes	No
Subject:		
Known diabetic	12	15
New diabetic	2	5

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#### Mortality in diabetic subjects.

##### 6.5: cause of death.

Death certificate details were also collected to examine the underlying cause of death, although I do accept that these causes may be very inaccurate [350].

Causes of death were grouped into ischaemic heart disease (including IHD itself and heart failure if no other cause was stated), cerebrovascular disease (including stroke, CVA, intracerebral haemorrhage), other vascular disease (involving peripheral vascular disease or ischaemic bowel), all malignancies with myeloma and pancreatic adenocarcinoma recorded separately since they seemed more common in diabetic subjects, respiratory system disease (generally lobar pneumonia and chronic obstructive airways disease), gastrointestinal disease (included a ruptured gall bladder and aspiration from a hiatus hernia), and other causes. The underlying cause was taken as the cause of death eg the cerebrovascular disease rather than the bronchopneumonia (due to immobility due to cerebrovascular disease).

The causes of death are given in Figure 6.12, but I feel that one particular death certificate must be recorded for posterity (Figure 6.11), since although the diagnosis of diabetes mellitus was recorded as contributing to the patient's death, the diabetes was only mild.

# Diabetes in the elderly.

Figure 6.11: copy of death certificate of Melton subject.

**D. Cert.**  
**SR.**

**CERTIFIED COPY**  
Pursuant to the Births and

**OF AN ENTRY**  
Deaths Registration Act 1953

**DEATH**

Entry Number **83**

Registration District **Melton Mowbray** Administrative area **County of Leicestershire**  
Sub-district **Melton Mowbray**

1. Date and place of death  
**Twentieth May 1989**  
**[REDACTED], Melton Mowbray**

2. Name and surname  
**[REDACTED]**

3. Sex **Female**

4. Maiden surname of woman who has married **WOODMAN**

5. Date and place of birth **1st December 1901**  
**Melton Mowbray**

6. Occupation and usual address  
**Widow of Horace [REDACTED], General Stores Proprietor (retired)**  
**[REDACTED] Melton Mowbray**

7. (a) Name and surname of informant  
**William Richard [REDACTED]**

(b) Qualification  
**Brother**

(c) Usual address  
**22 Doctors Lane, Melton Mowbray**

8. Cause of death  
I/a. **Gross Myocardial Fibrosis**  
b. **Atheroma of Coronary Arteries**  
II/. **Mild Diabetes Mellitus**  
Certified by **[REDACTED] M.B.**

9. I certify that the particulars given by me above are true to the best of my knowledge and belief.  
**W.R. [REDACTED]** Signature of informant

10. Date of registration  
**Twenty second May 1989**

11. Signature of registrar  
**R.M. Palmer Registrar**

*Richard [REDACTED]*  
Certified to be a true copy of an entry in a register in my custody.  
Superintendent Registrar **25 MAR 1993** Date  
**GA 496818**

Mortality in diabetic subjects.

Figure 6.12: table of causes of death.

	IHD	CVD	OVD	NG	RS	GIT	Other
<b>65 male:</b>							
Known DM	0	1	0	0	0	0	0
New DM	1	1	0	1	0	0	0
IGT	0	0	0	0	0	0	0
Normal	2	1	0	2	1	0	0
<b>65 female:</b>							
Known DM	2	0	0	0	0	0	0
New DM	0	0	0	1p	0	0	0
IGT	1	0	0	0	1	0	0
Normal	3	0	0	3	1	0	0
<b>70 male:</b>							
Known DM	1	1	1g	0	0	0	1H
New DM	0	0	0	0	0	0	0
IGT	0	1	0	0	0	0	0
Normal	2	1	0	1	1	0	0
<b>70 female:</b>							
Known DM	2	0	0	1m	0	0	0
New DM	0	0	0	0	0	0	0
IGT	0	0	0	0	0	0	0
Normal	2	1	0	0	0	0	0
<b>75 male:</b>							
Known DM	3	1	0	0	1	0	1t
New DM	0	0	0	0	0	0	0
IGT	0	0	0	0	1	0	0
Normal	1	2	0	3	0	0	0
<b>75 female:</b>							
Known DM	1	2	1b	1	0	0	0
New DM	0	0	0	0	0	0	0
IGT	0	0	0	0	0	0	0
Normal	2	1	0	2	0	0	1a
<b>80 male:</b>							
Known DM	2	0	0	0	1	0	0
New DM	0	0	0	1m	0	1	0
IGT	1	2	0	0	0	0	0
Normal	4	0	0	1	0	0	0
<b>80 female:</b>							
Known DM	1	0	0	0	0	0	0
New DM	0	0	0	0	0	0	0
IGT	0	0	0	0	0	0	0
Normal	2	1	0	2	1	1	1r
<b>85 male:</b>							
Known DM	1	1	0	0	0	0	0
New DM	0	0	0	0	0	0	0
IGT	0	0	0	1p	0	0	0
Normal	0	1	0	0	0	0	0
<b>85 female:</b>							
Known DM	0	0	0	0	0	0	0
New DM	1	0	0	0	0	0	0
IGT	0	0	0	0	0	0	1t
Normal	2	4	0	1	0	0	1d, 1v

Continued next page with key.



### Diabetes in the elderly.

Figure 6.12: table of causes of death (continued).

	IHD	CVD	OVD	NG	RS	GIT	Other
<b>All male:</b>							
All DM	8	5	1g	1, 1m	2	1	1H, 1t
Known DM	7	4	1g	0	2	0	1H, 1t
New DM	1	1	0	1, 1m	0	1	0
IGT	1	3	0	1p	1	0	0
Normal	9	4	0	7	2	0	0
<b>All female:</b>							
All DM	7	2	1b	1, 1m, 1p	0	0	0
Known DM	6	2	1b	1, 1m	0	0	0
New DM	1	0	0	1p	0	0	0
IGT	1	0	0	0	1	0	1t
Normal	11	8	0	8	2	1	1a, 1r, 1d, 1v
<b>Both sexes:</b>							
All DM	15	7	1g, 1b	2, 2m, 1p	2	1	1H, 1t
Known DM	13	6	1g, 1b	1, 1m	2	0	1H, 1t
New DM	2	1	0	1, 1m, 1p	0	1	0
IGT	2	3	0	1p	2	0	1t
Normal	20	12	0	15	4	1	1a, 1r, 1d, 1v

IHD = ischaemic heart disease.

CVD = cerebrovascular disease.

OVD = other vascular disease (g=gangrene of foot, b=ischaemic bowel).

NG = malignancy (m=myeloma, P=pancreatic)

Other causes: H=hypoglycaemic reaction, t=trauma, r=acute renal failure (cause unspecified), d=subdural haematoma, a=subarachnoid haemorrhage, v=aortic valve disease (cause unspecified).

The cause of death was compared amongst the different groups of glucose tolerance for all ages and sexes combined since the number of deaths was not large (99 in total). Examining all vascular disease, IHD, cerebrovascular disease, and other vascular disease revealed no increase in proportion of deaths due to these when comparing all diabetic subjects or all subjects with abnormal glucose tolerance to normal subjects (2 tailed Fisher's exact  $p > 0.135$ ).

However, it is known that morbidity due to macrovascular disease is more common in diabetic subjects [340,343] and that diabetic subjects with strokes [263,351,352] and myocardial infarctions [321-323] fare worse than their non-diabetic counterparts. Most other survival studies which have examined the cause of death also find increased mortality from IHD [23,44,123,328,330-332,334,336, 338,340-342,343,344], and cerebrovascular disease [328,330,331,336,338], although this increased risk from cerebrovascular disease is less than that from IHD, and not confirmed by other studies [44,332,334,340]. Thus I suspect that

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#### Mortality in diabetic subjects.

the number of deaths obtained from the Melton study population was not large enough to show excess macrovascular death.

There was no difference in proportion of deaths due to malignancy in the diabetic or abnormal glucose tolerant groups (2 tailed Fisher's exact  $P=0.294$ ); previous studies found either no increase in deaths due to malignancy in diabetic subjects [331], or a reduced risk of death due to malignancy [328,330,332,336,338]. It is most likely that any decrease in deaths due to malignancy in diabetic subjects is due to the phenomenon of "competing risk" ie that vascular disease is killing the subject before any malignancy [338].

The two subjects with pancreatic adenocarcinoma were a newly diagnosed diabetic male and a male with IGT. Some survival studies have shown an association between pancreatic adenocarcinoma and diabetes [328]; others have found an association between recently presenting diabetic subjects and pancreatic adenocarcinoma [353]. A recent review article concluded that both newly diagnosed and long standing diabetic subjects had an increased risk of pancreatic adenocarcinoma [354]. However, comparing diabetic plus IGT subjects to normal subjects for pancreatic adenocarcinoma revealed no association considering all deaths (2 tailed Fisher's exact  $P=0.186$ ), and only a weak possible association considering just deaths due to malignancy (2 tailed Fisher's exact  $P=0.071$ ). Thus I am unable to confirm an excess of pancreatic adenocarcinoma in the Melton subjects with abnormal glucose tolerance, but this could well be due to inadequate sample size.

The two subjects with myeloma included one new diabetic male and one known diabetic female. The known diabetic subject developed myeloma many years after her diabetes was diagnosed. The new diabetic male developed diabetes after his myeloma was diagnosed. It would be fascinating to invoke the Crow-Fukase syndrome [355] which has numerous other names [356] with the possibility that the monoclonal protein interfered with the insulin receptors to cause the diabetes; neither of these two subjects were taking steroids for their myeloma when the diabetes was diagnosed. In a series of 93 subjects with the Crow-Fukase

### Diabetes in the elderly.

syndrome, 26 were known to have "glucose intolerance", although what this exactly meant and how hard they looked is not stated [355]. Comparing diabetic to normal subjects for myeloma deaths revealed no association considering all subjects (2 tailed Fisher's exact  $P=0.14$ ) and possibly a weak association considering just deaths due to malignancy (2 tailed Fisher's exact  $P=0.0526$ ). Thus an outbreak of Crow-Fukase syndrome in Melton seems unlikely and I would need a bigger sample to demonstrate this. Diabetes is common in Crow-Fukase syndrome, but this syndrome is uncommon in the west and unlikely to account for many of the diabetic subjects in the UK.

Overall, no one cause of death predominated. It may well be that diabetic subjects do worse than normal subjects whatever other medical condition they acquire; for instance diabetic Dutch people had up to 90 times relative risk of fatal pneumonia following influenza infection compared to Dutch not known to be diabetic [357]

#### 6.6: which known diabetic subjects died?

Some data on the known diabetic subjects who died are available from Section 2.17, and are shown in Figure 6.13.

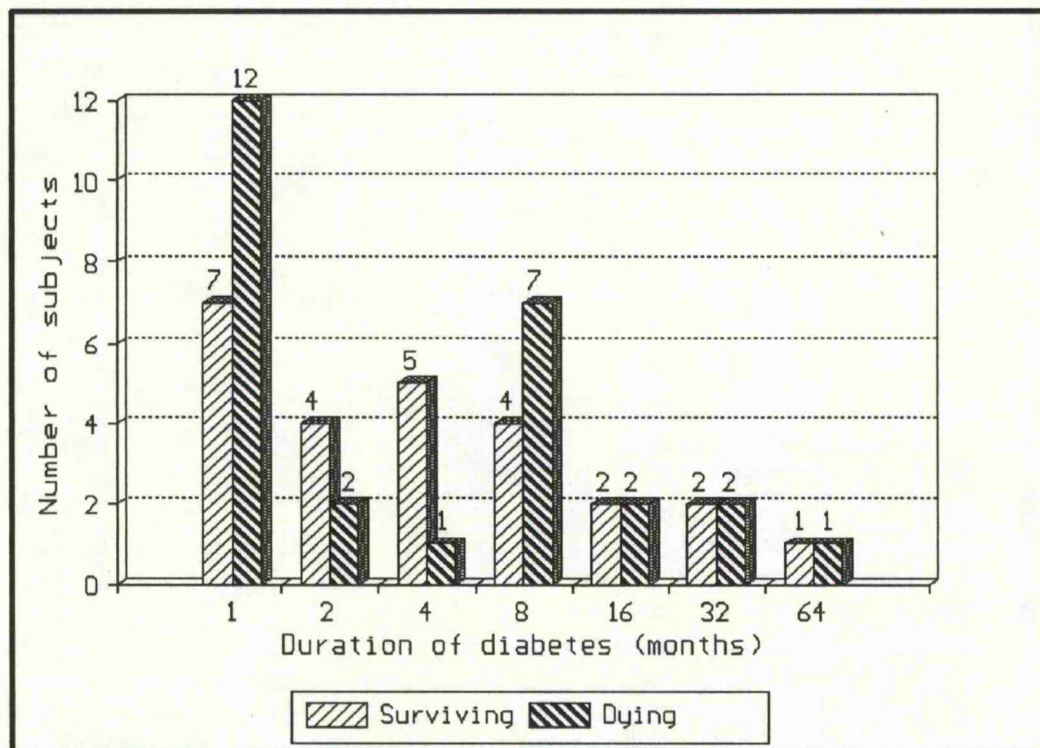
Figure 6.13: features of known diabetic subjects living and dying.

	Subjects surviving (n=25)	Subjects dying (n=27)
Male (number)	8	16
Median age (years) (range)	70 (65-85)	75 (65-85)
Duration DM: median (years) (range)	3 (0-53)	2 (0-36)
NIDDM (number)	22	23
Treatment (numbers)		
Insulin	5	5
Oral agents	13	9
Diet alone	7	9
None	0	4
Diagnosed by others after study onset (number)	1	4

### Mortality in diabetic subjects.

There was no difference in type of diabetes between subjects surviving and dying (2 tailed Fisher's exact  $P=1.0$ ), no difference in type of treatment ( $\text{Chi}^2=4.91$ ,  $\text{DF}=3$ ,  $P=0.18$ ), no difference whether treated or not (2 tailed Fisher's exact  $P=0.115$ ), and no difference regarding the small number who were diagnosed by other professionals during the study (2 tailed Fisher's exact  $P=0.351$ ). There was a slight difference in survival regarding gender, with more females amongst the survivors (2 tailed Fisher's exact  $P=0.058$ ).

Figure 6.14: histogram of duration of diabetes for known diabetic subjects living and dying.



The duration of diabetes in these subjects is shown in Figure 6.14; there was no difference in duration between those dying and those surviving (Mann-Whitney U test 2 tailed  $P=0.46$ ). However, it has been shown that duration of disease is an independent risk factor for death [329], but also an excess number of deaths occur in diabetic subjects in the first year after diagnosis [334]. It has also been noted that comorbidity at the time of diagnosis is important regarding survival [358], in



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### Diabetes in the elderly.

that subjects with no comorbidity experienced a 7% mortality over 5 years compared to a 58% mortality if vascular comorbidity was present in similarly aged subjects. Thus one wonders if some subjects were detected because of other medical conditions which might lead to a rapid demise, and other subjects also had a long duration of diabetes again leading to a rapid demise. Thus it may be that subjects dying tended to comprise those with both very long duration of diabetes, and those with short duration.

To test this, a 2 by 2 contingency table was constructed for alive or not versus presence in either of the end bars of histogram Figure 6.14; this revealed no tendency for the dying subjects to cluster at the extremes of disease duration (2 tailed Fisher's exact  $P=0.27$ ).

However, those surviving tended to be younger than those dying (Mann-Whitney U test 2 tailed  $P=0.061$ ), and this has been previously noted in Bedford [44].

#### 6.7: which newly diagnosed diabetic subjects died?

The basic demographic details regarding survival of subjects found to be diabetic is given in Figure 6.15.

Figure 6.15: demography of new diabetic subjects living and dying.

	Subjects surviving (n=11)	Subjects dying (n=7)
Male (number)	3	5
Median age (years) (range)	75 (65-85)	65 (65-85)

There was no difference in sex (2 tailed Fisher's exact  $P=0.15$ ), or age (2 tailed Mann Whitney U test  $P=0.50$ ) between those that died or survived.

Combining the sex difference in survival for both known and new diabetic subjects reveals that the male subjects are far more likely to die over the period of observation (2 tailed Fisher's exact  $P=0.016$ ; odds ratio 3.67, 95% CI 1.23-11.15).

### Mortality in diabetic subjects.

Further information on the new diabetic subjects was available from the data in Chapter 5, and is given in Figure 6.16.

Figure 6.16: features of new diabetic subjects living and dying.

	Male		Female	
	Alive (n=4)	Dead (n=5)	Alive (n=8)	Dead (n=2)
Never smoked	2	0	5	1
No of drugs:- 0	0	1	2	1
1	3	1	4	0
2+	1	3	2	1
Antihypertensive agent use	2	4	3	1
Systolic HT	1	1	4	1
HT or anti-HT use	3	4	7	2
Stroke	1	0	2	1
Angina	1	1	2	0
MI	3	1	1	0
Claudication	1	0	1	0
Cataract	1	2	3	1
Retinal A Occl	1	1	1	0
ECG codes:- 1:	2	1	1	0
3:	0	1	1	0
5:	2	1	2	0
6:	0	1	1	0
7:	0	1	1	1
8:	1	0	2	0

Amalgamating male and female subjects, because of very small numbers, revealed no association between death and any of the features of large vessel disease, hypertension, smoking, number of classes of drug used, cataracts or retinal artery occlusion, or abnormal ECG Minnesota codes (2 tailed Fisher's exact  $p>0.1$ ).

Previous studies have shown that diabetic subjects have an increased risk of death with cataracts [359], all forms of vascular disease [358], and hypertension [259]; in normal subjects retinal artery occlusion was also associated with premature death [278,280,282]. However, with only 19 new diabetic subjects to consider, it is unlikely that this small sample will reveal much about which factors within diabetic subjects forecast early mortality.

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### Diabetes in the elderly.

#### 6.8: conclusions.

Follow up of subjects in the Melton diabetic survey revealed that diabetes in the elderly is associated with a substantial mortality in Melton which is most marked at 65 years of age and decreases with age. Subjects with known diabetes were more likely to die than those with newly diagnosed diabetes who were more likely to die than those with IGT who were more likely to die than those with normal glucose tolerance.

The risk of death in diabetic subjects was higher than reported in previous studies and this was probably due to full ascertainment of glucose tolerance status in the subjects whose survival was being studied.

There was no particular cause recorded on the death certificates for this increased death rate; previous studies showed an increase in macrovascular disease as a cause of death, but I was unable to show this, probably due to the small sample size. Myeloma might have been commoner than expected as a cause of neoplastic deaths among the diabetic subjects.

Diabetes was infrequently recorded on the death certificates, although this may be a problem of the certificate rather than the certifying doctor.

The known diabetic subjects who died were older than the surviving known diabetic subjects, and female diabetic subjects were more likely to survive than male diabetic subjects.

Since the standardised mortality ratios for Melton were the same as the rest of the UK in 1981, since Melton is fairly typical of a UK population (Section 2.16), and since I believe that there is little recruitment bias (Chapter 3), I believe that these findings of high mortality in diabetic subjects have national significance.

Can anything be done to improve survival? As discussed in Section 4.1, Hayes *et al* demonstrated that hospital diabetic clinic attendance improved survival relative to GP clinic care [181]. Yudkin in a review article [138] concluded that the diabetic subject had far more to gain by attention to other cardiovascular risk factors, such as stopping smoking, taking aspirin and treating hypertension and dyslipidaemias, than non-diabetic subjects; indeed Harris has demonstrated a

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#### Mortality in diabetic subjects.

decline in diabetic cardiovascular mortality in recent years in the USA [139]. Increased cardiorespiratory fitness is associated with increased survival in diabetic subjects [360], although there is no evidence that the increased fitness directly causes the increased survival. Thus it may well be that just giving all diabetic subjects the best quality care and advice available will improve the survival of the group; unfortunately there may be delay in diagnosis, perhaps up to 7 years [361], after the onset of diabetes during which the patient is untreated. Finally, the high associated mortality is further evidence that diabetes in the elderly is not mild.

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## Diabetes in the elderly.

### **Chapter 7: management of the elderly diabetic person.**

#### **7.1: introduction.**

With 8.1 million elderly in England and Wales [3], and a prevalence of diabetes mellitus of approximately 9% in this age group as discussed in Chapter 2, there are many elderly diabetic subjects needing diabetic care.

The elderly diabetic may have several problems in looking after his diabetes. These patients often do not know the symptoms of hypoglycaemia [362] or appreciate that their medication can cause this; there is some evidence to suggest that the elderly non-diabetic subject does not develop hypoglycaemic symptoms until a much lower level than the young non-diabetic subject [363]. A survey of elderly IDDM patients in London confirmed that many did not understand hypoglycaemia, and also revealed that only 49% recognised some of the features of hyperglycaemia, and only 65% would react appropriately to obtain help [364]; 25% of these patients had been admitted to casualty with hypoglycaemia over the preceeding 12 months, and 78% had at risk feet due to neuropathy or vascular disease. Applying sticky spots to patients feet revealed that the elderly frequently cannot see or reach lesions on the soles of their feet [365]. Thus the elderly diabetic person needs a great deal of help to manage their illness.

Geriatricians are taking a larger role in the management of medical problems, particularly as part of integration with general medicine; with their expertise in managing the complex medical and social problems of the elderly, they should be well placed to manage the elderly person with diabetes [366]. It is therefore important to establish whether the diabetic care of the geriatricians differs from that of physicians with a special diabetic commitment. There have been no previous studies examining the diabetic care offered by geriatricians.

Similarly with the new general practitioner (GP) contract [226], GPs are playing a larger role in diabetic care, which is generally greatly valued by the patient because of continuity of care and local availability; GP care has been examined in several studies.

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#### Management of the elderly diabetic person.

When evaluating the quality of GP care of the diabetic, it is helpful to consider it in terms of structure, process, and outcome [367].

The structure of care was examined in Sheffield [368] when a survey of practices revealed that of 104 practices who would give information, 16 had a diabetic register and recall system, 15 screened eyes routinely, and 14 examined feet routinely; the diabetes nurse specialists then helped to set up the registers and design protocols but it is of note that when the audit was repeated after 2 years these figures had only increased to 82, 51, and 60 practices respectively.

In terms of process, surveys have generally been bleak. In Ipswich [369] GPs who expressed an interest in shared care were left to manage 209 patients for 2 years before a hospital clinic review at which time it was found that only 117 patients had had an entry in their cooperation books, 52 had had an eye examination, and 47 had had a random glucose measurement. The authors wondered if the main problem was organisation, or lack of it. One study from Southampton GPs [370] found that by using their practice nurse to coordinate review, the rate of fundoscopy increased from 27% to 80%, and the number of complications found needing referral in their 112 diabetic subjects increased from 5 per year to 19 - 25 per year.

A survey in Norwich [62], as in Southampton mainly GP led, found that the study practices who requested help in setting up mini-clinics achieved rates of fundoscopy and HbA<sub>1c</sub> measurement similar to hospital clinics; these practices were probably better than average since their initial follow up rate was 42% of all diabetic subjects and fundoscopy rate 40% whereas at the end of the 3 year evaluation comparative practices without help were reviewing only 1% of their diabetic patients. Despite their keenness, they only achieved fundoscopy rates of 82%, although their numbers of patients had increased from 190 to 386; it is salutary that the hospital fundoscopy rate was only 53%.

One further shared care initiative in London [372] found that fundoscopy rates were higher in hospital than general practice (79% versus 42%). So diabetic care

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### Diabetes in the elderly.

from GPs is very variable, depending on the individual GPs, and is not complete, although neither is the hospital care.

There are many other studies showing poor structure, process and general practitioner beliefs of diabetic care [373-376].

However, outcome is more important than other audit measures [367]. In the Wolverhampton mini-clinics [377] which see a carefully selected one third of all diabetic subjects, frequency and results of HbA<sub>1c</sub> and random blood glucose measurement are similar to hospital values for similar diabetic subjects (generally NIDDM). However, in Cardiff [181] it was found that discharging 103 stable type 2 diabetics, average age 60 years, to GPs resulted in more deaths (18 versus 6 of 97 hospital control subjects; Fisher's exact  $P=0.017$ ) and worse control (GP HbA<sub>1c</sub> 10.4% versus hospital HbA<sub>1c</sub> 9.5%;  $t=2.52$ ,  $P<0.02$ ). A three centre study [378] found that the variation in GP ability to detect sight threatening retinopathy was variable from 41% to 67%; the higher sensitivity was similar to the sensitivity of the hospital service studied, but at the expense of specificity. A further study showed that a selection of GPs could not detect significant retinopathy when compared to ophthalmologists [379] and called for specialisation within general practices; however, specialisation is abhorred by some GPs [61] since they wish to continue to care for all aspects of their patients.

One study from a Bristol GP [380] not only showed inadequate process and outcome, but also ignored subjects over 70 years old, which excluded 33% of their known diabetic subjects!

Thus overall GP care is very variable but in some instances, particularly if the GPs are organised in mini-clinics, GPs do as much as hospital based physicians (which has not always been fully comprehensive) [62,52] and, in selected patients, may achieve similar indices of diabetic control [377]. However, there are serious doubts about the very important aspect of screening for treatable retinopathy [378,379].

When setting up a diabetic clinic, it is recognised that background knowledge regarding diabetes was essential [381], but there has only been one study

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#### Management of the elderly diabetic person.

examining this [382]. This study looked at knowledge in the broad areas of diet, therapy, monitoring, and acute and chronic complications, where the GPs scored between 45 and 70%; the exact questions and responses are not given, but the GPs were in between medical students and hospital doctors in performance, and running a diabetic mini-clinic did not improve their score [382].

Thus a postal questionnaire was sent to both groups of hospital physicians and general practitioners to assess their knowledge of what I considered to be important common problems in the elderly diabetic person, such as the management of a new diabetic subject, the management of probable maculopathy, the management of diabetic neuropathic cachexia, and the choice of sulphonylurea.

One benefit of my slow writing is that there was time to repeat the audit in diabetologists and geriatricians, thus completing the audit cycle.

#### **7.2: method to survey geriatricians and diabetologists.**

From the Medical Directory [383], 100 acute hospitals were randomly picked using a computer program to produce random page numbers; the local geriatrician and diabetic specialist were identified. The geriatricians were identified by the title of geriatrician or physician in care of the elderly; the diabetic specialists were identified by either being in charge of the diabetic clinic or by membership of the British Diabetic Association. This group of diabetic specialists could include those who merely "inherited" the diabetic clinic to those that were full time diabetologists. All were sent a questionnaire comprising three case histories with questions on the management of a new type 2 diabetic patient, a patient with painful neuropathy, and a patient with probable maculopathy; these were followed by questions on choice of sulphonylurea therapy and use of home blood glucose monitoring in the elderly. The questionnaires were sent in January and February 1988. The full questionnaire is given in Appendix 4.

To try and improve the response rate, the covering letter stated that any publications would appear in the geriatric press, and, on the second set sent to



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geriatricians, the letter was co-signed by Professor CM Castleden of the Leicester geriatric department.

Results were analysed using a 2 tailed Fisher's exact P test unless otherwise stated.

#### **7.3: the geriatricians' and diabetologists' response rate.**

Of the 100 questionnaires in each group, I received replies from 54 geriatricians and 81 diabetic specialists, over 6 months; this difference in response rate was significant ( $P < 0.0001$ ), and perhaps indicates less interest in diabetes amongst the geriatricians. Unfortunately, the replies were anonymous and therefore all the geriatricians were sent a further copy of the questionnaire with an explanatory letter. In future anonymous questionnaire studies, I will either have each questionnaire individually coded with the code nominally held by my secretary, or simply use an invisible ink pen such as 'ghost writer' from the Early Learning Centre to label the questionnaires. Re-balloting the geriatricians produced 3 duplicate replies, 2 unfilled replies (one only sees patients aged 75+, one had retired), 2 that had not received the initial posting, they claimed, and 16 new replies; during this period, 3 more replies from diabetologists were received. Thus in total replies were received from 84 diabetologists and 72 geriatricians.

Eleven geriatricians replied that their patients were older than those discussed in the questionnaire and therefore the questions were not relevant, although fortunately they did complete the questionnaires. One diabetologist wrote that the patients were not geriatric patients, but the bread and butter of the diabetic and general medical clinics.

The first and second ballots of geriatricians produced similar replies with no statistically significant difference, and the two sets of responses were analysed together. I will now consider each part of the questionnaire in turn.

#### Management of the elderly diabetic person.

##### 7.4: case 1; a newly diagnosed diabetic patient.

*Case 1: a 68 year old lady (height 5'6", weight 11st 3lb) presents with asymptomatic glycosuria and a random blood sugar of 14.4 mmol/l. She takes bendrofluzide 10 mg daily for hypertension: history otherwise unremarkable.*

*There were then questions regarding examination, investigation, treatment and follow up of this patient.*

This first case represented a patient with a common problem, ie an overweight probable type 2 diabetic subject on a thiazide diuretic. The exact criteria for the diagnosis of diabetes had not been met, since she was asymptomatic [51]; the other feature of note was her diuretic which may have provoked her diabetes. The responses of the hospital physicians are given in Figure 7.1.

Figure 7.1: management of a probable newly found diabetic subject.

Would you?		Number of diabetologists answering yes n=84	Number of geriatricians answering yes 1st : 2nd reply:reply n=56: n=16
Measure visual acuity	****	62	23 : 4
Perform fundoscopy		83	55 : 15
Dilate the pupils	****	65	22 : 5
Measure BP lying		75	53 : 14
Measure BP sitting	**	40	40 : 13
Examine vibration sense at the ankles	****	77	42 : 8
Examine the peripheral pulses		83	54 : 16
Examine the shoes		43	32 : 9
Measure the glycosylated haemoglobin		43	31 : 7
Measure the creatinine +/- LFTs		72	46 : 13
Treat with diet alone	(a)	19	10 : 2
Treat with oral hypoglycaemics		2	4 : 0
Treat with diet & change antihypertensive		62	42 : 14
When stable, discharge to GP	(b) **	46	41 : 11
When stable, follow her up yourself	(c) *	38	14 : 5

a) One diabetic specialist wanted confirmation of her diabetes and thus did not treat her.

b) 2 of the geriatricians and 18 of the diabetic specialists would discharge to the GP depending on the GP; one geriatrician would refer her to the diabetic clinic for follow up.

c) 3 diabetologists used shared care to follow her up themselves.

\*, p<0.05, \*\*, p<0.025, \*\*\*, p<0.01, \*\*\*\*, p<0.001

### Diabetes in the elderly.

Geriatricians and diabetic specialists looked at the optic fundus equally frequently, but differed in their method of assessment. The geriatrician was less likely to dilate the pupils ( $P<0.0001$ ) or measure the visual acuity ( $P<0.0001$ ) compared to the diabetologist. These techniques [384-386] are recommended because the elderly diabetic patient commonly has retinopathy at presentation [276]. Since elderly subjects often have senile miosis, one is wasting one's time and providing inadequate care by performing fundoscopy without mydriasis.

Both groups were just as likely to measure the blood pressure (BP) lying; the geriatrician was more likely also to measure it sitting ( $P=0.0018$ ). Of the major hypertension trials in the elderly, SHEP, MRC, and EWPHE [137,300,298] used seated BP, and STOP used supine BP [299]; all showed a reduction in cerebrovascular disease on treating the hypertension. There are no major studies comparing treatment or not of supine or seated BP. The geriatricians' use of seated BP probably reflects the difficulty in getting some older patients onto an examination couch, I feel.

The geriatricians were less likely to test for vibration sense at the ankles ( $P=0.00042$ ) since it is so often absent in the elderly, they argued. Most would examine the peripheral pulses but only 54% of all respondents would examine the shoes. It is important to pay attention to all facets of foot care in all diabetics, but particularly the elderly since those having amputations are commonly old and the elderly have more extensive amputations [35]; it is thought that well fitting footwear is an important factor in preventing foot ulceration [38,387,388] and it is known that elderly women in particular often wear bad shoes [389].

Both groups were just as likely to measure the liver function tests and creatinine which would have been necessary later if metformin or a sulphonylurea was used [390].

Both groups measured the glycosylated haemoglobin equally frequently; treatment in the form of diet and changing the thiazide was an easy first step, and therefore the  $HbA_1$  was an unnecessary expense.

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76% would treat the lady with a diet and change/review antihypertensive medication, which follows the consensus view that diet should be tried first [51,326,391]. 4 geriatricians would initiate oral hypoglycaemics before a trial of diet; although this is not statistically significant ( $P=0.42$ ), it has been pointed out that this is clinically significant [392], and that the offending practitioners should go on an update course.

Once the patient was controlled, the diabetologist was more likely to follow her up and the geriatrician was more likely to discharge her to GP care ( $P=0.031$ ). GP care is discussed in the introduction to this chapter and examined later.

#### 7.5: case 2: a patient with diabetic neuropathic cachexia.

*Case 2: a 69 year old man (height 5'10", weight 11st 5lb) has been diabetic for 10 years controlled on diet alone. His weight is normally 12st.; he complains of pains in his feet at night. Examination revealed foot pulses present, absent ankle jerks, vibration sense absent below iliac crests and his soles were tender to touch. Investigations showed a glycosylated haemoglobin of 10.8% (4-8.5%) and random blood sugar of 15 mmol/l.*

There then followed several choices of treatment for this patient with a painful peripheral neuropathy, and the replies are given in Figure 7.2.

Figure 7.2: management of painful peripheral neuropathy.

Would you?	Number of diabetologists answering yes n=84	Number of geriatricians answering yes 1st : 2nd reply:reply n=56: n=16
Would treat the patient with insulin ****	53	20 : 5
Would use insulin immediately	20	5 : 3
Would use paracetamol **	15	18 : 7
Would use antidepressants ***	33	13 : 1
Would use anticonvulsants	23	16 : 5

\*:  $p<0.05$ , \*\*:  $p<0.025$  \*\*\*:  $p<0.01$ , \*\*\*\*:  $p<0.001$

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### Diabetes in the elderly.

This second patient, an elderly man with painful peripheral neuropathy, weight loss and poor diabetic control represents diabetic neuropathic cachexia [393]. The recommended treatment is insulin [394,395]; 35% of geriatricians would use it compared to 62% of diabetologists ( $P=0.00069$ ); both were just as unlikely to use insulin straight away ( $P=0.058$ ).

Treatment of the pain of diabetic neuropathy is difficult; double blind crossover trials show improvement using phenytoin [396], carbamazepine [397], and tricyclic antidepressants (TCAs) [398,399], but the consensus view is that tricyclic antidepressants are probably best after strict metabolic control [400]. The geriatrician was more likely to use paracetamol ( $P=0.018$ ) and was less likely to use TCAs ( $P=0.0086$ ) than the diabetologist.

These studies on the treatment of neuropathic pain have included subjects of all ages. From my diabetic clinics in Sheffield, routine questioning revealed 14 subjects with neuropathic pain (median age 75, range 65 to 85 years) who were treated with amitriptyline; 8 subjects were unable to tolerate low doses of 25mg to 50mg and only one subject experienced relief of pain and tolerated the TCA. Most of the patients had already tried simple analgesics such as paracetamol with no help. Thus the management in the elderly must focus on pristine glycaemic control and simple measures such as bed cradles.

Two diabetologists and one geriatrician wrote suggesting further investigation into weight loss, which is interesting in that Rifkin and Ellenberg's textbook, "Diabetes Mellitus", suggests in one chapter that one should [401], and in another that one should not [402]!

Similarly one of each group wanted to look for other causes of neuropathy, which, given the multiple pathology in the elderly is probably wise with simple investigations. Again from my diabetic clinics in Sheffield, routine questioning revealed 25 subjects with neuropathic pain (again median age 75, range 65 to 85 years as above) in whom simple tests revealed chronic myeloid leukaemia (1 subject), vitamin B<sub>12</sub> deficiency (2 subjects), hypothyroidism (3 patients) and

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pancreatic adenocarcinoma (1 subject); whether these comorbid conditions had anything to do with the painful neuropathy is another matter.

#### 7.6: case 3: management of diabetic maculopathy.

*Case 3: a 70 year old lady with type 2 diabetes complains of poor vision. She consulted an optician who reported that one year previously her visual acuity (VA) was 6/6 both eyes, but now is reduced to 6/12 and 6/9; there are no cataracts but there are "changes at the back of the eye". Fundoscopy revealed hard exudates above and lateral to the macula in the right eye (VA 6/9) and background changes but macula apparently normal in the left eye (VA 6/12).*

The doctor was then asked if he/she would dilate the pupils and if he/she would refer the patient for photocoagulation; the replies are given in Figure 7.3.

Figure 7.3: management of patient with probable maculopathy.

Would you?	Number of diabetologists answering yes n=84	Number of geriatricians answering yes 1st : 2nd reply: reply n=56: n=16
Would dilate the pupils	*** 75	40 : 12
Would not dilate but would refer on	9	12 : 4
Would refer to ophthalmologist	**** 77	38 : 12
Would not dilate eye or refer on	* 0	4 : 0

\*: p<0.05, \*\*: p<0.025, \*\*\*: p<0.01, \*\*\*\*: p<0.001

This third patient represents a diabetic with probable macular disease, who needs photocoagulation if this is the case. Maculopathy is a potentially preventable cause of blindness; 2.6 times more people become blind from maculopathy than proliferative retinopathy [30] each year in the UK; thus care of the elderly diabetic subject's eyes is of high priority for health care of the elderly [32].

The geriatrician was less likely to dilate the pupils (P=0.0074) and less likely to refer the patient to an ophthalmologist (P=0.00042). It is important to dilate the pupils, particularly in the elderly with senile miosis, and to measure the visual acuities to detect macular involvement at an early stage, since it is so amenable to

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#### Diabetes in the elderly.

photocoagulation to preserve vision; this is most effective if the visual acuity is 6/12 or better [33,34,384]. Macula oedema presents with a falling visual acuity and a grey rippling of the macula which is difficult to identify; its presence is also indicated by hard exudates encircling the macula; one must emphasise that without mydriasis, one is unlikely to see anything at or around the macula.

However, in this case, one would want to refer the patient for an ophthalmological opinion whether one found the maculopathy or not since maculopathy may be extremely hard to detect. If one is faced with a diabetic patient with falling visual acuities, one would almost invariably refer the patient to the ophthalmologist for assessment even if the reason was not apparent, although the correct diagnosis would enable the ophthalmologist to prioritise his referrals. In this case the optician's report gives all the information needed, and the patient could have been referred to the ophthalmologist without further examination or delay. It is very worrying that when faced with a patient whose vision was deteriorating, many geriatricians (30.6%) did not refer the patient for an expert opinion, although the question was actually "would you refer to an ophthalmologist for photocoagulation?".

It is also worrying that 4 geriatricians when faced with this patient neither referred the patient to the ophthalmologist nor dilated the pupil, although all the diabetologists did at least one of these ( $P=0.043$ )

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### 7.7: the geriatricians' and diabetologists' choice of sulphonylurea.

The choice of sulphonylurea was investigated by asking the physicians which sulphonylurea they would use in the over 70's, and the responses are given in Figure 7.4.

Figure 7.4: the choice of sulphonylurea.

		Number of diabetologists n=84	Number of geriatricians 1st : 2nd reply:reply n=56: n=16
Tolbutamide	***	31	10 : 0
Glibenclamide	****	13	27 : 7
Glipizide		8	6 : 2
Gliclazide	*	10	1 : 1
Chlorpropamide		2	0 : 0
Gliquidone		0	1 : 1
Several including glibenclamide (a)		5	8 : 4
Several not inc. glibenclamide		15	0 : 1
"None", "short acting", Metformin		0	3 : 0

a) Some replies consisted of a short list of sulphonylureas.

\*: p<0.05, \*\*: p<0.025, \*\*\*: p<0.01, \*\*\*\*: p<0.001

There was a marked difference in favoured sulphonylurea with the diabetic specialists preferring a short acting agent such as tolbutamide ( $P=0.0017$ ) or gliclazide ( $P=0.038$ ), whilst the geriatricians preferring glibenclamide ( $P<0.0001$ ). Comparing use of glibenclamide or chlorpropamide by the geriatricians (46) to that by the diabetic specialists (20) reveals a massive difference in prescribing habits ( $P<0.00001$ ). Several geriatricians preferred glibenclamide for reasons of compliance but if there is poor compliance with tablets, there will probably be poor compliance with diet. Even 2.5mg of glibenclamide caused fatal hypoglycaemic reactions [403] in the classic paper on glibenclamide induced hypoglycaemia. Because it may accumulate in deep storage compartments [404], and because its metabolites are renally excreted and hypoglycaemic themselves [405], glibenclamide may cause hypoglycaemic reactions for 72 hours after the last dose [406]. Recent reviews recommend short acting sulphonylureas [391,407,408] such as tolbutamide (also inexpensive), glipizide, gliquidone, and gliclazide but hypoglycaemic reactions have occurred on these also, stressing the



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need to be certain that they are necessary [409]. It is perhaps odd that 2 diabetic specialists preferred chlorpropamide. However, studies do suggest that chlorpropamide is less likely to cause hypoglycaemic reactions than glibenclamide [408,410,411]; glibenclamide itself is highly potent with a 3 hour half life and its metabolites are less hypoglycaemic [405], which gives glibenclamide a very fierce onset of action unlike chlorpropamide with a long half life, inactive metabolites and gentle onset of action.

### 7.8: the geriatricians' and diabetologists' use of home blood glucose monitoring in the elderly.

Finally, the opinion of the physicians was sought regarding the statement "home blood glucose monitoring by elderly patients themselves, is rarely practical or necessary", and their agreement or disagreement with this is documented in Figure 7.5. One diabetologist wrote "Of course I do - I wrote it!", and several other replies could be traced to their author by virtue of covering letters, colour ink, or postmark; thus the survey was not as anonymous as intended.

Figure 7.5: "home blood glucose monitoring by elderly patients themselves, is rarely practical or necessary".

	Number of diabetologists answering yes  n=84	Number of geriatricians answering yes 1st : 2nd reply: reply n=56: n=16
Agree	32	24
No strong feelings	19	12
Disagree	29	17

The results do not total the number of respondents since some did not select a choice, but instead wrote a short essay on the topics of elderly, practicality and generalisations; seven diabetologists commented that this depends on the individual elderly person being considered.

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There was no difference between the two groups in their opinion ( $\chi^2=0.623$ ;  $DF=2$ ;  $P=0.73$ ). Although the benefits of blood glucose monitoring in the elderly and in subjects with NIDDM are open to debate [412-414], it is important that no one group of physicians is prejudiced against the elderly patient's access to blood glucose monitoring.

#### **7.9: completing the audit cycle of geriatricians and diabetologists: methods.**

Thus this original audit survey of the geriatricians' and diabetologists' management of the elderly diabetic subject revealed that geriatricians were using excess glibenclamide and were not dilating pupils for fundoscopy; not surprisingly, they were less expert on specialised topics eg diabetic neuropathic cachexia.

The study was presented at the 1989 spring British Geriatrics Society meeting and reported in Age and Ageing [415, see Annexe 1]; since then relevant information has appeared in Drugs and Therapeutics Bulletin, Geriatric Medicine, and Care of the Elderly; a BGS diabetic special interest group now exists.

To see if the management of the elderly diabetic had improved, a further questionnaire study was performed in late 1992. As in the original study questionnaires were randomly sent to 100 geriatricians and 100 diabetologists picked from the 1992 Medical Directory.

Only 3 questions were asked:-

- 1: Which sulphonylurea would you use in the elderly?
- 2: Would you routinely dilate the pupils of a new diabetic subject?
- 3: Would you discharge a stable diabetic to their GP?

The questionnaire can be seen in Appendix 4.

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### 7.10: completing the audit cycle of geriatricians and diabetologists: results and discussion.

Results were compared to the original 1988 survey (Table 7.6) using Fisher's exact test (2 tails).

Figure 7.6 results completing the audit cycle (number of respondents).

	Glibenclamide use	Dilate pupils	Discharge to GP
Geriatricians 1988 (n=72)	46	27	52
Geriatricians 1992 (n=70)	9	33	38
Diabetologists 1988 (n=84)	18 <sup>a</sup>	65	46
Diabetologists 1992 (n=86)	2 <sup>b</sup>	78	39

<sup>a, b</sup>: a further 2 & 1 diabetologists would use chlorpropamide respectively.

In 1988, the geriatricians' initial response rate was 54%; in 1992 this rate had increased to 70% ( $P=0.029$ ); possible explanations include greater interest, different time of year, or shorter questionnaire.

The geriatricians' choice of sulphonylurea swung dramatically from glibenclamide to the short acting agents, tolbutamide, gliclazide and glipizide, over the 4 year interval ( $P<0.00001$ ) and now resembles the use of shorter acting agents by diabetologists in 1988 ( $P=0.1$ ).

From 1988 to 1992 the diabetologists used even less glibenclamide ( $P=0.0004$ ), and still use less than today's geriatricians ( $P=0.013$ ), although this difference is not so great if chlorpropamide use is included ( $P=0.036$ ). Avoidance of glibenclamide is now recommended in the British National Formulary [416]. A new problem is that glipizide, used by 15 diabetologists and 12 geriatricians, is far more likely to cause hypoglycaemia in the elderly than the young, despite being short acting [417]. However, there are no adequate studies showing whether glipizide is more likely to cause hypoglycaemia than tolbutamide or gliclazide,

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particularly in the elderly. In 1988 8 of each group of physicians used glipizide, but this trend in increased usage is not significant ( $P=0.1$ ).

The geriatricians' rate of mydriatic use has remained static ( $P=0.308$ ) and is still less than the diabetologists' use in 1988 ( $P=0.00019$ ) and 1992 ( $P<0.00001$ ).

Originally the geriatrician was more likely than the diabetologist to discharge a stable diabetic to the GP, but the geriatrician is now less likely to discharge than in 1988 ( $P=0.036$ ), with a similar rate to the diabetologists of 1988 ( $P=0.1$ ) and 1992 ( $P=0.33$ ). The diabetologists' discharge practice has not changed ( $P=0.28$ ).

Of 32 geriatricians following up diabetic subjects, 18 would dilate pupils and 26 would avoid glibenclamide; of 38 geriatricians discharging diabetic subjects, 15 would dilate the pupils and 35 would avoid glibenclamide; these 2 groups of geriatricians do not differ in approach ( $p>0.1$ ). Geriatricians' sulphonylurea use has improved dramatically, but geriatricians who endeavour to follow up diabetic subjects should become familiar with dilated fundoscopy.

#### **7.11: general practitioners' management of the elderly diabetic person: method.**

To examine the GPs' knowledge, the same questionnaire as originally sent to the geriatricians and diabetologists was sent to 100 GPs randomly selected from the 1992 Medical Directory in early 1993. The questionnaire (see Appendix 4) also asked whether the GP's practice ran a diabetic clinic, and whether the GP participated on this; the GP was also given the opportunity in most questions to refer the patient to a diabetologist.

To try to improve the response rate, the covering letter was also signed by Dr C Wayne OBE, President of the Royal College of General Practitioners, and the letter stated that any publications would appear in the GP press.

3 replies were returned uncompleted; one GP had disappeared without trace, one had become an immunologist, and one would have nothing to do with the survey since my co-worker was a fundholding GP. A further 3 questionnaires were sent out and in total 71 were returned completed.

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There were 3 different types of GP relating to diabetic clinic participation; no diabetic clinic (NN), practice diabetic clinic but did not participate (YN), and practice diabetic clinic participant (YY). Results were analysed by comparing results for the 3 different types of GP within themselves and to the reference responses from the earlier replies of the diabetic specialists in 1988.

#### 7.12: general practitioners' management of the newly diagnosed diabetic.

The general practitioners responses' to the questions on the management of the newly diagnosed diabetic subject (see Section 7.4) are given in Figure 7.7 with the diabetologists' figures for comparison.

Figure 7.7: the GPs' management of a probable newly found diabetic subject.

Would you?	Number of diabetologists answering yes n=84	Number of GPs answering yes:		
		NN n=23	YN n=21	YY n=27
Measure visual acuity	62	10	11	22
Perform fundoscopy	*** 83	20	18	22
Dilate the pupils	**** 65	2	7	13
Measure BP lying	**** 75	2	2	0
Measure BP sitting	**** 40	20	19	22
Examine ankle vibration sense	**** 77	7	10	20
Examine the peripheral pulses	* 83	20	20	25
Examine the shoes	43	8	7	10
Measure the HbA <sub>1c</sub>	* 43	9	18	21
Measure the creatinine +/- LFTs*	72	13	16	22
Treat with diet alone (a)	19	2	4	3
Treat with oral hypoglycaemics	2	2	1	1
Treat with diet & change antiHT	62	19	16	23
Refer to diabetologist	--	4	2	1

\*: p<0.05, \*\*: p<0.025, \*\*\*: p<0.01, \*\*\*\*: p<0.001

Two general practitioners stated that they would have an optician measure the visual acuity, and these are included as having checked the visual acuity.

Despite the GPs measuring the visual acuity as often as the diabetologists (P=0.087), they were far less likely to perform fundoscopy (P=0.0013), or dilate the pupils (P<0.00001); the importance of these has been pointed out in Sections 7.4 and 7.6. Again as with the geriatricians, 10 GPs would not look in the eyes or refer to diabetologist (NN=3, YN=2, YY=5), which is extremely disconcerting.

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GPs often feel that they have inadequate knowledge, but successful diabetic eye courses have been run [418] leading to improved GP ability with the ophthalmoscope, and perhaps these should become more widespread. The GPs participating in diabetic clinics were more likely to check the VA ( $P=0.006$ ), and dilate the pupils ( $P=0.019$ ) than the other 2 groups of GPs, but they still omitted to examine the fundi in much the same way as the other GPs.

As with the geriatricians, the GP was less likely to measure the BP lying ( $P=1.29E^{-28}$ ), and more likely to measure it sitting ( $P<0.0001$ ) than the diabetologist.

The GPs overall were less likely to examine for vibration sense at the ankle ( $P<0.0001$ ), and less likely to examine the foot pulses ( $P=0.048$ ), although the majority of the GPs did examine the foot pulses; again there was no great difference in numbers examining the shoes ( $P=0.052$ ), since very few from either group did this. GPs participating in diabetic clinics were more likely to examine for vibration sense at the ankles ( $P=0.0066$ ) than the other GPs, but no more examined the foot pulses.

The GPs were slightly more likely to measure the  $HbA_{1c}$  than the diabetologist ( $P=0.049$ ), and slightly less likely to measure the LFTs and creatinine ( $P=0.046$ ). As already stated, the  $HbA_{1c}$  is superfluous, but the LFTs and creatinine are essential when considering oral hypoglycaemic treatment (Section 7.4). The GPs with diabetic clinics (not necessarily participating) were far more likely to check the  $HbA_{1c}$  ( $P=0.00084$ ), than the GPs without a diabetic clinic; this might have more to do with the ease of getting blood samples analysed rather than differences in beliefs.

Again as with the geriatricians, 4 GPs said they would commence oral agents and not refer to a diabetologist (NN=2, YN=1, YY=1), which is clinically but not statistically significant.

There were no differences between the three groups of GPs regarding referral to diabetologist ( $\chi^2=2.6$ ; DF=2;  $P=0.27$ )

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### 7.13: general practitioners' management of diabetic neuropathic cachexia.

The general practitioners' responses to the questions on the management of the subject with diabetic neuropathic cachexia (see Section 7.5) are given in Figure 7.8 with the diabetologists' figures for comparison.

Figure 7.8: the GPs' management of painful peripheral neuropathy.

Would you?	Number of diabetologists answering yes n=84	Number of GPs answering yes:		
		NN n=23	YN n=21	YY n=27
Treat the patient with insulin****	53	0	0	1
Use insulin immediately****	20	0	0	1
First try weight reduction****	0	4	7	4
First use sulphonylurea***	33	11	13	21
First use biguanide***	0	4	1	1
Use paracetamol	15	3	8	3
Use antidepressants***	33	3	4	5
Use anticonvulsants	23	3	4	5
Refer to diabetologist at start--	--	14	8	10
Refer to diabetologist later--	--	5	6	9

\*:  $p < 0.05$ , \*\*:  $p < 0.025$  \*\*\*:  $p < 0.01$ , \*\*\*\*:  $p < 0.001$

Again as in the geriatricians, the GPs were far less likely to use insulin at all ( $P=3.56E^{-18}$ , or initially ( $P=0.00024$ ) when compared to the diabetologist; it has previously been shown that GPs are very unhappy with prescribing insulin [375], and since most of the GPs (45% initially and a further 28% later) referred the patient to the diabetologist, they may well have been expecting the diabetologist to start the insulin.

Again the GP was far less likely to prescribe tricyclic antidepressants to the patient ( $P=0.0025$ ), but was just as unlikely to prescribe anticonvulsants ( $P=0.13$ ), or paracetamol ( $P=0.84$ ) as the diabetologist.

There was no difference between the three groups of GPs regarding further referral to the diabetologist ( $\chi^2=1.6$ ;  $DF=2$ ;  $P=0.45$ ).

Again seven GPs wished to look for other causes of weight loss and the patient's deterioration.

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## 7.14: general practitioners' management of the patient with maculopathy.

The general practitioners' responses to the questions on the management of the patient with probable maculopathy (see Section 7.6) are given in Figure 7.9 with the diabetologists' figures for comparison.

Figure 7.9: the GPs' management of patient with probable maculopathy.

Would you?		Number of diabetologists answering yes n=84	Number of GPs answering yes:		
			NN n=23	YN n=21	YY n=27
Would dilate the pupils	****	75	9	12	17
Refer to ophthalmologist	****	77	9	17	15
Refer to diabetologist	- -	0	16	7	13
Neither dilate eye or refer on *		0	3	0	1

\*: p<0.05, \*\*: p<0.025 \*\*\*: p<0.01, \*\*\*\*: p<0.001

As with the geriatricians, the GP was far less likely to dilate the pupils (P<0.0001), or refer to an ophthalmologist (P<0.0001) compared to the diabetologist. The GPs had the option of referring the patient to the diabetologist and 36 did this. however, there were still 4 GPs who would neither refer the patient for specialist help, nor dilate the pupils, which is significantly more than the diabetologists (P=0.04), but similar to the geriatricians.



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#### 7.15: general practitioners' choice of sulphonylurea.

The GPs' choice of sulphonylurea (see Section 7.7) are given in Figure 7.10 with the diabetologists' figures for comparison.

Figure 7.10: the GPs' choice of sulphonylurea.

Would you?	Number of diabetologists answering yes n=84	Number of GPs answering yes:		
		NN n=23	YN n=21	YY n=27
Tolbutamide	31	6	1	10
Glibenclamide	13	7	6	1
Glipizide	8	1	3	1
Gliclazide	*** 10	7	7	9
Chlorpropamide	2	0	2	0
Several inc glibenclamide (a)	5	2	0	2
Several not inc glibenclamide *	15	0	0	4
Metformin	0	0	2	0

a) Some replies consisted of a short list of sulphonylureas; .  
\*: p<0.05, \*\*: p<0.025 \*\*\*: p<0.01, \*\*\*\*: p<0.001

Overall there was no difference between the GPs and diabetologists regarding the use of short acting agents and avoidance of glibenclamide/chlorpropamide (P=0.366); the GPs were more likely to use gliclazide and the diabetologists were more likely to use the other short acting agents. Interestingly, participating in a diabetic clinic compared to not participating (ie YY versus YN and NN) was associated with less use of a long acting sulphonylurea (P=0.015).

Figure 7.11: trends in use of long acting sulphonylurea drugs.

Subjects	Glibenclamide/chlorpropamide use	
	Number	Percentage (95% CI)
Geriatricians 1988 (n=72)	46	64 (52-75)
Geriatricians 1992 (n=70)	9	13 (6-23)
Diabetologists 1988 (n=84)	20	24 (15-34)
Diabetologists 1992 (n=86)	3	2 (0.7-9.9)
GPs 1992 (n=71)	20	28 (18-40)

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#### Management of the elderly diabetic person.

However, it is now apparent that the other physicians have reduced their use of the longer acting sulphonylureas, so that both geriatricians ( $P=0.036$ ) and diabetologists ( $P<0.0001$ ) use significantly less long acting sulphonylureas than the GPs.

#### 7.16: general practitioners views on home blood glucose monitoring.

The GPs' views on the use of home blood glucose monitoring by elderly patients (see Section 7.8) are given in Figure 7.12 with the diabetologists' figures for comparison.

Figure 7.12: "home blood glucose monitoring by elderly patients themselves, is rarely practical or necessary"; GPs' views.

Would you?	Number of diabetologists answering yes n=84	Number of GPs answering yes:		
		NN n=23	YN n=21	YY n=27
Agree	32	9	7	9
No strong feelings	19	7	5	7
Disagree	29	7	9	11

There was no difference between the diabetologists and GPs regarding the use of home blood glucose monitoring ( $\text{Chi}^2=0.4$ ;  $\text{DF}=2$ ;  $P=0.82$ ). As discussed in Section 7.8, it is good that no one group of doctors discriminates more than the others against the elderly.

#### 7.17: conclusions.

In summary, there were of course many similarities between the three groups of physicians regarding the management of the elderly diabetic patient, but there were particular differences on eye problems, treatment of painful diabetic neuropathy, and use of oral hypoglycaemic agents; mismanagement of these problems will lead to increased morbidity and decreased quality of life.

Taking the diabetologists' responses as the gold standard, which may not be the optimum management eg in not examining footwear, the geriatricians

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demonstrated important deficiencies in assessing the eyes of a newly diagnosed diabetic subject, in assessing and referring a subject with probable maculopathy, in the management of diabetic neuropathic cachexia and in choice of sulphonylurea.

On repeating the audit, the geriatricians improved their care of the elderly diabetic patient over a 4 year period by avoiding glibenclamide. They may also have been more interested in the problem since the response rate was greater and they were less likely to discharge the patient to the GP. However, they were still not routinely dilating pupils for fundoscopy despite its recommendation, which is a serious omission.

Similarly on comparing general practitioners to diabetologists, the GPs were not assessing the eyes of new diabetic subjects or subjects with probable maculopathy correctly, and had difficulty with managing diabetic neuropathic cachexia. Their use of sulphonylureas was similar to the previous use by diabetologists, but still tended to include excess long acting agents compared to the geriatrician and diabetologist of 1992. Interestingly, GPs who participated in diabetic clinics used a much safer selection of sulphonylurea, were more likely to check the visual acuity ( $P=0.006$ ), and more likely to dilate the pupils ( $P=0.019$ ) compared to GPs who did not participate in a diabetic clinic; otherwise there were no differences between the groups of GPs.

This study does show that the geriatricians' and general practitioners' knowledge was poor when compared to the diabetic specialists' knowledge. This might be due to several causes.

It is not surprising that the diabetic specialist is more knowledgeable than someone with a far broader field of interest. The field of geriatric medicine is so vast, that it is difficult to keep up to date in all branches of medicine; however, review articles on the elderly diabetic often occur in the geriatric press. Recent editions of Pathy's and Brocklehurst's textbooks contain useful chapters on diabetes, but these are reference works rather than bedtime reading; many of the references which I quote are, or should be, regular reading such as the Drug and Therapeutics Bulletin and Geriatric Medicine. Similarly the field of general

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practice is even larger than that of geriatric medicine, but again the information is available in Drugs and Therapeutics Bulletins, and there has been an excellent symposium in *The Practitioner* in 1991 [419].

I believe that the full significance of the elderly diabetic is underestimated in terms of both numbers and morbidity (see Chapters 1,2,5,6). Despite this, I feel that many geriatricians and GPs still equate NIDDM. with "mild" diabetes (see Figure 6.11). Finally, perhaps some find the subject of diabetes uninteresting, but armed with greater knowledge, this might change.

Although it is not surprising that diabetic specialists wish medical practitioners to achieve a certain standard of excellence [420], the British Diabetic Association also expects this standard [421], as do the Medical Defence Union [422] and the law courts [423].

From a practical point of view, there are very many elderly diabetic patients who may have transport problems (approximately 70% of patients attending the Sheffield geriatric diabetic clinic need ambulance transport) and one would wish to minimise their travelling. Thus it would be best to consider GP and hospital care as complementary, offering two opportunities to identify problems, rather than mutually exclusive and antagonistic. Various shared care protocols have been pioneered in different UK centres, tailored to local circumstances [377,424,425]. The differences between GPs participating and not participating in GP mini-clinics, and the geriatricians' improvement over 4 years suggest that doctors other than diabetologists have the potential to contribute to patient care if trained. Provided that the clinician primarily responsible for the patient's diabetic care was identified and protocols for shared care are implemented, greater involvement of the geriatrician and GP should increase the number of diabetic subjects receiving adequate care. However, many general practitioners and geriatricians are lacking in relevant knowledge at present.

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### Diabetes in the elderly.

#### Chapter 8: summary.

The impact of diabetes on the elderly of the United Kingdom is probably underestimated. This thesis aims to describe the prevalence of diabetes in the elderly following population screening since diabetes is often undetected in the elderly, associated specific and non-specific diabetic complications at diagnosis, mortality associated with various categories of glucose intolerance in the elderly, and deficiencies in the management of these diabetic subjects.

Previously the prevalence of diabetes in the elderly was calculated from the number of known diabetic subjects. To allow for the undiagnosed diabetic subjects, the prevalence of diabetes mellitus was investigated in a sample of elderly aged 65 to 85 years, representative of the British elderly population, using a modified oral glucose tolerance test (MOGTT) and 1985 WHO criteria. Of the sample of 863, 52 had previously been diagnosed diabetic; 585 consented to be tested and 19 were found to be diabetic. The prevalence of previously diagnosed diabetes was 6% (95% CI 4.3-8.1%), and the prevalence of previously undiagnosed diabetes in those receiving an MOGTT was 3.3% (95% CI 1.9-5.0%). 159 spouse of similar age were examined and 6 had diabetes (prevalence 3.8% (95% CI 1.4-8.0%). This prevalence is similar to recent figures obtained from Coventry and Islington. There was no sex difference in prevalence of diagnosed or previously undiagnosed diabetes; the overall prevalence of diabetes did increase from 65 years of age (prevalence 6.3% (95% CI 3.5-10.3)) to 85 years (13.8% (95% CI 4.6-30.4%)), but the significance of this is uncertain due to the small sample size. Impaired glucose tolerance was more prevalent in males (10.4% (95% CI 6.9-14.9%)), than females (5.4% (95% CI 3.2-8.4%)), significantly so (2 tailed Fisher's exact  $P=0.027$ ). The high prevalence of previously diagnosed diabetes in this study might be due to the long-standing community diabetic care in the area studied. Reinterpreting data from screening surveys in the 1960's from Birmingham and Istock suggests that the overall

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### Diabetes in the elderly.

prevalence of diabetes has not changed, but that more of the subjects are recognised nowadays.

Sociodemographic variables, and cognitive function were compared in subjects who did, and did not agree to participate in the diabetes screening survey. There was no difference in social class, sex, self-health rating, or utilisation of health services. There was no difference in subsequent mortality in those that did and did not participate in the survey. The recruitment rate did decline with an increase in age, but there did not appear to be a significant change in diabetes prevalence with age. Examining subjects aged 75 or more, non-respondents were more likely to be have a low score on testing cognitive function; however, on closer examination, this was because the older subjects were more likely to refuse MOGTT and more likely to have cognitive impairment which in itself was not actually associated with refusal. Interestingly, subjects with known diabetes were more likely to have cognitive impairment compared to normal glucose tolerant subjects, and newly diagnosed diabetic subjects were less likely to have cognitive impairment than normal subjects. Thus the effect of non-recruitment to the survey probably had little effect on the prevalence of diabetes obtained.

The ability to easily screen for diabetes would be invaluable. Serum fructosamine was compared to the MOGTT as a tool for detecting diabetes in the community. Because fewer diabetic subjects were found than anticipated, it was necessary to include spouses in evaluating fructosamine as a detection tool. 742 residents of the Melton Mowbray area aged between 65 and 85 years were screened (subjects in the main survey and their spouses), measuring glucose and fructosamine on the blood sample taken 2 hours after a 75g glucose load. The fructosamine concentration in 264 normal subjects had a Gaussian distribution (mean=1.67mmol/l, SD=0.13mmol/l).

25 new diabetic subjects were found; 23 had fructosamine measured; 17 had values above the 95th percentile and 4 more had values above the 90th percentile. Thus at the 95th percentile fructosamine demonstrates a sensitivity of 74%,

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### Diabetes in the elderly.

specificity of 94.6%, and at the 90th percentile, the sensitivity is 91%, specificity 88.5%.

Examining the use of a glycosylated haemoglobin level elevated above the accepted normal range in the diabetic subjects and a similar number of normal subjects revealed a sensitivity of 63%, and specificity of 91%; the glycosylated haemoglobin is an expensive test to perform.

Examining the use of any degree of glycosuria detected by standard urinalysis testing sticks revealed a sensitivity of 52%, and specificity of 94%; these sticks are very inexpensive.

Thus the fructosamine concentration was found to be a useful screen for diabetes but this may be dependant upon the fructosamine assay used, the definition of diabetes used, and the population studied; it may have a place in the routine screening of the elderly to detect a group for further investigation by MOGTT.

The newly diagnosed diabetic subjects were compared to a control group of normal subjects.

Of 24 newly diagnosed diabetic subjects (main survey sample plus spouses combined), only 7 had diabetic symptoms which were unlikely to be present in subjects aged over 78 years.

These diabetic subjects did not have an increased BMI compared to the control group, but of the 10 diabetic subjects aged 65 to 74, 10 were below median height for their normal controls (1 tailed Fisher's exact  $P=0.054$ ).

There was evidence of specific diabetic complications: 1 diabetic subject had background retinopathy and decreased or absent ankle tendon reflexes were more likely in the new diabetic subjects compared to controls (odds ratio 4.4, 95% CI 1.5-13.1).

Non-specific complications were also present such as cataract (odds ratio 4.7, 95% CI 1.6-14.2), and present or previous carpal tunnel syndrome (odds ratio 9.7, 95% CI 1.5-66.7).

Considering vascular disease, any abnormality of glucose tolerance (diabetes plus IGT) was associated with previous stroke (odds ratio 5.9, 95% CI 1.3-27.5), and

### Diabetes in the elderly.

intermittent claudication (odds ratio 5.9, 95% CI 1.04-32.8). New diabetes singly was associated with retinal artery occlusion (odds ratio 68.5, 95% CI 4.2-301), and angina (odds ratio 4.6, 95% CI 1.3-16.8). The association between hypertension and its treatment and diabetogenic treatment was convoluted, probably because thiazide diuretics are a common drug in both classes of agents; both antihypertensive use (odds ratio 4.5, 95% CI 1.8-10.8) and diabetogenic drug use (odds ratio 4.8, 95% CI 1.8-13) were similarly associated with new diabetes.

Thus at this early stage of their disease, the new diabetic subjects had evidence of both specific and non-specific complications. Thus medical staff need to be aware of the likelihood of diabetes in an elderly person with specific or non-specific complications, and this reinforces the high associated morbidity with diabetes.

To investigate the effect of glucose tolerance status on mortality in the elderly, the subjects from the diabetes survey were followed for 4½ years by collection of their death certificates from Office of Population Censuses and Surveys.

Over 4½ years, death occurred in 27 of 52 known diabetic subjects, 7 of 19 newly diagnosed diabetic subjects, 9 of 44 IGT subjects, and 57 of 520 normal subjects.

A Cox's proportional hazards model was used to assess the relative risk of death for these subjects, and results are in Figure 8.1.

Figure 8.1: mortality of subjects with various degrees of glucose intolerance and different ages compared to normal glucose tolerant peers of similar age.

Subject:age (years)	Relative risk (95%CI)	
Known DM:all ages	5.2	(3.2-8.5)
New DM:all ages	3.0	(1.3-6.6)
All DM:all ages	4.5	(2.9-7.0)
IGT:all ages	1.7	(0.8-3.5)
Refused:all ages	1.5	(1.001-2.4)
All DM/ 65	12.12	(3.51-41.81)
All DM/ 70	4.74	(1.37-16.36)
All DM/ 75	6.96	(2.99-16.21)
All DM/ 80	2.48	(0.78-7.86)
All DM/ 85	1.34	(0.37-4.93)

Note: DM=diabetes; IGT=impaired glucose tolerance.



### Diabetes in the elderly.

There was no predominant cause of death recorded on the certificates of the diabetic subjects.

In the known diabetic subjects, younger subjects were more likely to survive than older subjects; combining known and new diabetic subjects revealed that male subjects were more likely to die (odds ratio 3.7, 95% CI 1.2-11.2). Duration, type, and treatment for diabetes seemed to have no significant effect on survival.

These figures for mortality in diabetic subjects are higher than previously believed, possibly because the normal group did not have subjects with undiagnosed diabetes or IGT confounding the picture.

The management of elderly diabetic patients by 100 Geriatricians and 100 Diabetologists, was assessed by a postal questionnaire in 1988. Replies were initially received from 54 Geriatricians and 81 Diabetologists ( $P=0.000074$ ); Geriatricians were re-balloted increasing replies to 71. The Geriatricians were less likely to check the visual acuities ( $P<0.00001$ ), less likely to dilate the pupils for fundoscopy ( $P<0.01$ ), less likely to refer a patient with maculopathy to an ophthalmologist ( $P=0.00042$ ), more likely to discharge a stable diabetic to GP care ( $P=0.031$ ), less likely to use insulin ( $P=0.00069$ ) or antidepressants ( $P=0.0086$ ) in treating painful peripheral neuropathy, and more likely to use glibenclamide instead of a short acting sulphonylurea ( $P<0.00001$ ).

As part of the audit cycle, geriatricians and diabetologists were re-examined after a 4 year interval; fewer geriatricians were using long acting sulphonylureas than previously ( $P<0.00001$ ) and fewer were discharging the diabetic patient to GP care (0.036); however, they were still using more long acting sulphonylureas than the diabetologists of that time (0.036) and were still not dilating the pupils for fundoscopy (0.00019).

The care given by general practitioners (GPs) was assessed by similar questionnaire in 1992 and compared to the diabetologists' replies. Again the GP was far less likely to either dilate the eyes ( $P<0.00001$ ), routinely perform fundoscopy ( $P=0.0013$ ), use insulin for diabetic neuropathic cachexia ( $P<0.00001$ ), or correctly manage a subject with probable maculopathy by

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#### Diabetes in the elderly.

referral to an ophthalmologist ( $P < 0.00001$ ). The GPs avoidance of long acting sulphonylureas was similar to the diabetologists of 1988, but still less than the geriatrician or diabetologist of 1992.

GPs who actually participated in diabetic clinics were more likely to use a safer sulphonylurea, check visual acuity and dilate pupils compared to their peers who did not participate in a clinic.

Thus the prevalence of diabetes in the elderly at 9% is higher than the frequently quoted prevalence of diagnosed diabetes of 3%. Even when detected early by screening, the elderly diabetic person already has evidence of increased macrovascular complications, peripheral neuropathy and cataract. These subjects also show a dramatic increase in mortality compared to normal subjects over a short 4½ year period. The management of these subjects' diabetes by geriatricians and general practitioners entails too little attention to correct eye examination and safe sulphonylurea use which would contribute to the morbidity of the disease.

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Diabetes in the elderly.

**Appendix 1: recruitment letters for diabetic survey.**

1: recruitment letter for Asfordby.

2: recruitment letter for other villages.

3: recruitment letter for town of Melton Mowbray.

DIABETIC RESEARCH DEPARTMENT

Leicester General Hospital  
Leicester  
LE5 4PW

Telephone Leicester 490490

LATHAM HOUSE MEDICAL PRACTICE

Sage Cross Street  
Melton Mowbray  
Leics LE13 1NX

Telephone Melton Mowbray 60101

Dear Sir/Madam

We would like to give you (and all other 65 year olds) a health check to see whether you have high blood pressure or sugar diabetes.

This would help us know whether we should be doing this to all people in the U.K. upon their retirement.

It would help you in that if you had either of these 2 conditions, it is better to know about it sooner rather than later.

We would like to do this by giving you some lucozade one morning, asking a few questions, doing a heart tracing and taking a small blood sample, at Melton Memorial. Transport would be provided if needed.

You are under no obligation to do this but the more people that agree, the more meaningful the survey will be.

If you want more details, you can write to or ring Dr S. Croxson (home phone no Leics 713525), Mrs M. Bodington (home phone no Melton 840677) or Dr T. Smith at Latham House.

We will contact you sometime over the next year (there are a lot of people in Melton) with a request to come and see us at Melton Memorial Hospital, to arrange to give you the lucozade and to answer any questions.

If you do not wish us to contact you, please could you write back and tell us so (you can leave the note at Latham House); we would like to know your reasons if possible.

Yours sincerely

Dr Simon Croxson  
Research Registrar

Mrs Maggie Bodington  
Diabetic Health visitor

Diabetic Department  
Leicester General Hospital  
Leicester LE5 4PW  
Telephone Leicester 490490

LATHAM HOUSE MEDICAL PRACTICE  
Sage Cross Street  
Melton Mowbray  
Leics LE13 1NX  
Telephone Melton Mowbray 60101

Dear Sir/Madam,

It is a well-known fact that many people have diabetes without ever being aware of it. People with diabetes may feel fit but nonetheless it is a health hazard and can in some people, even lead to blindness and amputations. Diabetes is the commonest form of treatable blindness in this country.

Some years ago people in middle age were checked to see if they had diabetes and now we would like to check your age group. This is done by a blood test. We would also like to check your blood pressure.

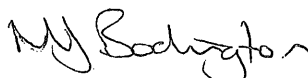
If you would like more details, you can write to or ring Dr S Croxson (home number Leics 713525) Mrs M. Boddington (home number Melton 840677) or Dr T Smith at Latham House.

We will contact you sometime over the next year. If you do not wish us to contact you, please could you write back and tell us so (you can leave the note at Latham House) we would like to know your reasons if possible.

Yours sincerely,



Dr Simon Croxson



Mrs Maggie Boddington (Health Visitor)

Diabetic Department  
Leicester General Hospital  
Leicester LE5 4PW

Telephone: Leicester 490490

Latham House Medical Practice  
Sage Cross Street  
Melton Mowbray  
Leics LE13 1NX  
Telephone: Melton Mowbray 60101

Dear Mrs. French,

It is a well-known fact that many people have diabetes without ever being aware of it. People with diabetes may feel fit but nonetheless it is a major health hazard which may lead to eye and circulation problems if undetected.

The most certain way of testing for diabetes is by a blood test after drinking a sugary drink. We would like to test you for diabetes and also check your blood pressure.

You do not have to do anything; we will contact you sometime over the next 2 months. If you do not wish us to contact you, please could you write back and tell us so (you can leave the note at Latham House) we would like to know your reasons if possible.

If you would like more details, you can write to or ring  
Dr S Croxson (home number Leics 713525), Mrs M Bodington (home number Melton 840677) or Dr T Smith at Latham House.

Yours sincerely



Dr Simon Croxson

Mrs Maggie Bodington  
(Health Visitor)

Mrs Jackie Button  
(Research Assistant)

PS

This is not funded by the National Health Service, but is free.

P.P.S.

The test is done in Melton.

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### Diabetes in the elderly.

#### **Appendix 2: diabetogenic drugs.**

What drug therapy is diabetogenic? Many drugs elevate the blood glucose level, but thiazide diuretics, diazoxide, streptozotocin and glucocorticosteroids are particularly potent [426]. Some treatments are rather esoteric or uncommon and unlikely to be seen in clinical practice in the elderly, such as lysergide, marijuana, L-aspariganase, isoniazid and pentamidine; others are used in only short courses such as nalidixic acid, and some treatment is unlikely to occur nowadays such as indomethacin, or overtreatment with thyroxine; however, other drug use is increasing such as oestrogen therapy, which is diabetogenic [427].

Figure A3.1 gives the list from NDDG document on diabetes classification [50], with extra drugs from the above two references added, and Figure A3.2 shows drugs accepted as increasing glucose levels in the British National Formulary [416], confirmed in the ABPI data sheet compendium.

All diuretics are diabetogenic generally, but bumetanide, and indapamide do not appear to be so in standard doses used [428-430].

All  $\beta$ -blockers are diabetogenic; the cardioselective  $\beta$ -blockers are less diabetogenic than the remainder, but are still diabetogenic [431-432]

All steroids elevate blood glucose levels. Topical application may avoid this; high dose inhaled steroid, eg beclomethasone 2000 mcg per day does not appear to alter glucose homeostasis [433], but steroid creams stronger than hydrocortisone or eumovate still cause some metabolic upset [416].

Non-steroidal anti-inflammatory drugs (NSAIDs) have been implicated in hyperglycaemia; indomethacin is acknowledged in the BNF and data sheet compendium to elevate blood glucose levels. Other NSAIDs such as ibuprofen, naproxen, diclofenac, ketoprofen, fenbufen, azapropazone are not indicated as having this problem. Reports to the Committee on Safety of Medicines [personal communication] on adverse effects of diclofenac from 1963 to 1990 include 4 reports of hyperglycaemia; thus it may be a slight problem, but has not been noted as a significant problem.

### Diabetes in the elderly.

Since calcium acts to help insulin release from pancreatic  $\beta$ -cells, it would not be surprising if they altered glucose homeostasis, but this seems to be a problem only with nifedipine, and not with verapamil, diltiazam, or nicardipine [431,432,434].

Figure A2.1: diabetogenic drugs from NDDG criteria.

#### **A: definite.**

Thiazides, chlorthalidone, metolazone  
Frusemide, ethacrynic acid  
Clonidine, diazoxide

ACTH, glucocorticosteroids  
Thyroxine in thyrotoxic doses  
Oestrogens, oral contraceptive

Haloperidol  
Lithium carbonate  
Phenothiazines (chlorpromazine, perphenazine)  
Tricyclic antidepressants (amitriptyline, desimipramine,  
doxepin, imipramine, nortriptyline)

Catecholamines  
Phenytoin  
levodopa  
 $\beta$ -blockers

Aspirin and paracetamol in overdose quantities  
Indomethacin

Isoniazid  
Nalidixic acid  
Pentamidine

Nicotinic acid

#### **B: Possible culprits.**

Bumetanide, clopamide

Calcitonin, medroxyprogesterone, megestrol acetate

Clopendixol

Fenoterol

Morphine

Cimetidine



### Diabetes in the elderly.

Figure A2.2: diabetogenic drugs from British National Formulary.

All diuretics except bumetanide, indapamide, spironolactone
All $\beta$ -blockers
All sympathomimetic agents eg adrenaline, isoprenaline, salbutamol (except standard inhaler doses) & diethylpropion
All steroids unless inhaled, or low strength ointment (eumovate)
Diazoxide
Nifedipine, but not other calcium antagonists
Nicotinic acid and derivatives
Thymoxamine
Amitriptyline, and probably other tricyclic antidepressants
Chlorpromazine in large doses, and probably other phenothiazines
Pyrazinamide
All sex steroids including oestrogens, progestagens, anabolic steroids
L-dopa
Indomethacin
Danazol
Phenytoin

Thus I will label steroids and thiazide diuretics as 'severely' diabetogenic [426], ignore drugs which are not used in clinical practice today, and label the remainder of diabetogenic drugs from the lists A3.1 and A3.2 as 'mildly' or 'probably' diabetogenic; this is fairly arbitrary and done for my convenience in analysing the data pertaining to patients seen.

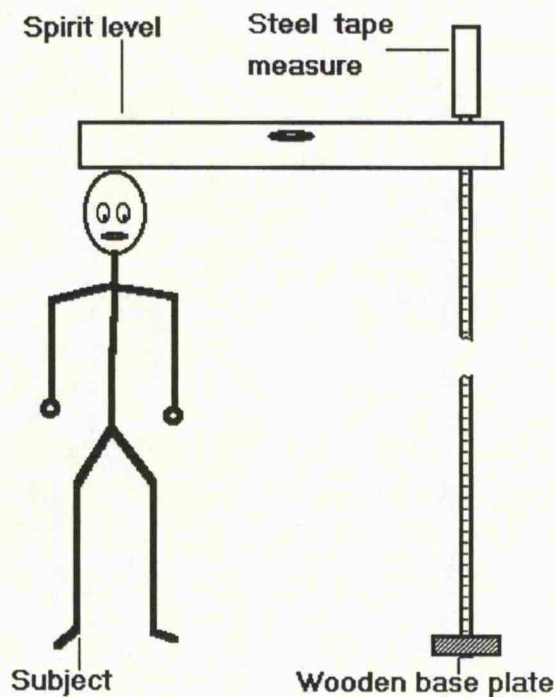
### Height measuring device.

#### Appendix 3: the height measuring device.

As discussed in Chapter 5, a device was constructed from a flexible steel rule, spirit level, piece of wood and some aluminium sheet to easily and practically measure the height (see Figure A3.1, A3.2).

In use, the subject stood upright on a hard floor with shoes off, looking directly forward; the examiner held the base plate on the floor with his foot, held the spirit level horizontal on the patient's head, and read the height from the rule.

Figure A3.1: construction of height measuring device.



Diabetes in the elderly.

Figure A3.2: photograph of height measure in use.



Diabetes in the elderly.

**Appendix 4: questionnaire survey questionnaires.**

1: Initial geriatrician and diabetologist questionnaire (geriatricians' copy).

2: Second geriatrician and diabetologist questionnaire (geriatricians' copy).

3: general practitioner questionnaire.

THE GERIATRICIANS ATTITUDE TO THE MANAGEMENT OF THE ELDERLY  
DIABETIC

A 68 year old lady (height 5'6", weight 11st 3lb) presents with asymptomatic glycosuria and a random blood sugar of 14.4 mmol/l. She takes bendrofluazide 10 mg daily for hypertension: history otherwise unremarkable.

Please answer Yes or No

Would you: Measure visual acuity (corrected)?.....

Perform fundoscopy?.....

Dilate the pupils?.....

Measure BP lying?.....

Measure BP sitting?.....

Examine vibration sense at the ankles?.....

Examine the peripheral pulses?.....

Examine the shoes?.....

Measure the glycosylated Hb?.....

Measure the LFTs and creatinine?.....

Regarding treatment, would you:

Diet alone?.....

Oral hypoglycaemics?.....

Diet and change anti-hypertensive therapy?.....

After 4 months, her diabetes and hypertension are well controlled.

Would you:

Discharge her to her GPs care?.....

Follow her up yourself?.....

A 69 year old man (height 5'10", weight 11st 5lb) has been diabetic for 10 years controlled on diet alone. His weight is normally 12 st; he complains of pain in his feet at night.

On examination: Fundoscopy normal

BP 140/80

Foot pulses present

Absent ankle jerks

Vibration sense absent below iliac crests

Soles tender when touched

Investigations show:

Glycosylated Hb 10.8% (Normal=4-8.5)

Random blood sugar 15 mmol/l

What would be your choice of treatment? Tick your choice

Further weight reduction .....

Sulphonylurea therapy .....

Biguanide therapy .....

Insulin therapy .....

Paracetamol .....

Any other .....

He was treated with glibenclamide 15 mg daily but 6 weeks later the pain was just as bad, despite further weight reduction to 10 st 11 lbs. Urinalysis was persistently negative and random blood sugar was 9.4 mmol/l.

What would you do now? Tick your choice

Add in metformin .....

Change to insulin .....

Prescribe carbamazepine .....

Prescribe amitriptyline .....

Any other .....

A 70 year old lady with NIDDM complains of poor vision. She consulted an Optician who reported that one year previously her vision was 6/6 in both eyes, but is now reduced to 6/12 and 6/9; there are no cataracts but there are "changes at the back of the eye".

Would you dilate the pupils? .....

Fundoscopy reveals:

Right eye (VA 6/9)-hard exudates above and lateral to the macula.

Left eye (VA 6/12)- background changes but macula appears normal.

Would you refer her for photocoagulation? .....

In the over 70 years age group, which sulphonylurea would you use?

.....

"Home blood glucose monitoring by elderly patients themselves is rarely practical or necessary"

Regarding this statement, do you	<u>Tick your choice</u>
Agree	.....
No strong feelings	.....
Disagree	.....

---

THE GENERAL PRACTITIONERS APPROACH TO THE ELDERLY DIABETIC PERSON

Please answer Yes or No

Does your practice run a diabetic clinic.....

Do you personally run a diabetic clinic.....

A 68 year old lady (height 5'6", weight 11st 3lb) presents with asymptomatic glycosuria and a random blood sugar of 14.4 mmol/l. She takes bendrofluazide 10 mg daily for hypertension: history otherwise unremarkable.

Please answer Yes or No

Would you: Measure visual acuity (corrected)?.....

Perform fundoscopy?.....

Dilate the pupils?.....

Measure BP lying?.....

Measure BP sitting?.....

Examine vibration sense at the ankles?.....

Examine the peripheral pulses?.....

Examine the shoes?.....

Measure the glycosylated Hb?.....

Measure the LFTs and creatinine?.....

Regarding treatment, would you:

Diet alone?.....

Oral hypoglycaemics?.....

Diet and change anti-hypertensive therapy?.....

Would you refer her to a diabetologist for follow-up?.....



A 69 year old man (height 5'10", weight 11st 5lb) has been diabetic for 10 years controlled on diet alone. His weight is normally 12 st; he complains of pain in his feet at night.

On examination: Fundoscopy normal

BP 140/80

Foot pulses present

Absent ankle jerks

Vibration sense absent below iliac crests

Soles tender when touched

Investigations show:

Glycosylated Hb 10.8% (Normal=4-8.5)

Random blood sugar 15 mmol/l

What would be your choice of treatment? Tick your choice

Further weight reduction .....

Sulphonylurea therapy .....

Biguanide therapy .....

Insulin therapy .....

Paracetamol .....

Refer to diabetologist .....

Any other (what?) .....

He was treated with glibenclamide 15 mg daily but 6 weeks later the pain was just as bad, despite further weight reduction to 10 st 11 lbs. Urinalysis was persistently negative and random blood sugar was 9.4 mmol/l.

What would you do now? Tick your choice

Add in metformin .....

Change to insulin .....

Prescribe carbamazepine .....

Prescribe amitriptylline .....

Refer to diabetologist .....

Any other (what?) .....

A 70 year old lady with NIDDM complains of poor vision. She consulted an Optician who reported that one year previously her vision was 6/6 in both eyes , but is now reduced to 6/12 and 6/9; there are no cataracts but there are "changes at the back of the eye".

Would you dilate the pupils? .....

Fundoscopy reveals:

Right eye (VA 6/9)-hard exudates above and lateral to the macula.

Left eye (VA 6/12)- background changes but macula appears normal.

Would you refer her for photocoagulation? .....

Would you refer her to a diabetologist? .....

In the over 70 years age group, which sulphonylurea would you use?

.....

"Home blood glucose monitoring by elderly patients themselves is rarely practical or necessary"

Regarding this statement, do you Tick your choice

Agree .....

No strong feelings .....

Disagree .....

Many thanks for taking the time and trouble to complete this questionnaire.

Geriatricians' management of Diabetes

1. Which sulphonylurea would you use  
in patients aged over 70?

.....

2. Would you routinely dilate the pupils of  
newly found diabetic subjects?

YES / NO

3. Do you follow-up stable diabetic subjects  
for their diabetes?

YES / NO

Thank you for your help.

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### **Annexe 1: publications from this work.**

The following articles are included from this research:-

Croxson S, Burden A, Bodington M, Botha H.  
The prevalence of diabetes in the elderly.  
Diabetic Medicine 1991; 8: 28-31.

Croxson S, Absalom S, Burden AC.  
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Croxson S, Burden AC, Castleden CM.  
Care of the elderly person with diabetes: a questionnaire study  
comparing Geriatricians versus Diabetic specialists.  
Age and Aging 1990; 19: 390-394.

Croxson S, Williams RP, Burden AC.  
Care of the elderly person with diabetes:  
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Croxson SCM, Jagger C.  
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## ORIGINAL ARTICLES



# The Prevalence of Diabetes in Elderly People

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The prevalence of diabetes mellitus was investigated in a sample of people aged 65 to 85 years, using a modified oral glucose tolerance test and 1985 WHO criteria. Of the sample of 861, 52 had previously been diagnosed diabetic; 583 consented to be tested and 19 were diabetic. The prevalence of previously diagnosed diabetes was 6.0 (95 % CI 4.3 to 8.1) %, and the prevalence of previously undiagnosed diabetes was 3.3 (95 % CI 2.0 to 5.0) %. The high prevalence of previously diagnosed diabetes might be due to the longstanding community diabetes care in the area studied.

KEY WORDS Diabetes mellitus Epidemiology Glucose tolerance test Elderly

## Introduction

With an increasing number of elderly people in the United Kingdom, it is important to ascertain the total prevalence of diabetes in that group, so that consequent health care can be planned. The reported prevalence of diagnosed diabetes in the elderly varies from around 3 % in Southall, Poole, and Oxford to 9 % in Leicester.<sup>1-4</sup> This, however, is the prevalence of diagnosed diabetes, and the total prevalence of diabetes including previously undiagnosed diabetes, would probably be higher.

The total prevalence of diabetes has been ascertained in some Western countries by population screening with modified oral glucose tolerance tests, and this rate varies from 7.6 % in 67-year-old Swedes, 17.9 % in White Americans aged 65 to 74 years, 23.6 % in Dutch over-65-year-olds, to 30 % in elderly Finns.<sup>5-8</sup> There have been two previous screening surveys in the UK using modified OGTTs and recent WHO criteria.<sup>9</sup> One was performed on a sample drawn from a general practice in Islington,<sup>10</sup> where the prevalence of previously undiagnosed diabetes in the elderly was 4 % and a similar number were already known to be diabetic, but only 75 % of people in the Islington survey were North European Caucasians, with the remainder almost equally Afro-Caribbean or Mediterranean in origin. In Coventry, a screening survey using an OGTT with pre-selection by a random blood glucose estimation found a prevalence of approximately 7.3 %. However, the Coventry survey looked at one of the most underprivileged areas in the UK.<sup>11</sup>

A diabetes screening survey has therefore been performed to define total prevalence in a more representative sample of British elderly, using the town of Melton Mowbray and its environs, which together resemble the age, sex, and social class structure of the UK (Tables 1, 2).<sup>12</sup>

Table 1. Age groups as a percentage of the whole population based on OPCS data<sup>12</sup>

	Over 75 years	Over 65 years Male	Over 60 years Female
Melton Mowbray	4.4	4.3	9.7
England and Wales	4.8	5.1	11.3

Table 2. Social class as a percentage of the whole population according to OPCS data<sup>12</sup>

	Melton Mowbray	Great Britain
Social class		
1	6	5
2	14	20
3	52	50
4	20	18
5	9	7

## Methods

All the people around Melton Mowbray attend on general practice which maintains an accurate computerized age/sex register, and a diabetes register derived from General Practitioner and Diabetic Health Visitor records. This age/sex register was set up in 1980 in conjunction with the Leicester University Department of Community Health;<sup>13</sup> the register was based on GP records, but these were checked by field workers while creating the register, and during several surveys of elderly people. The practice staff check the patients' detail whenever the patients attend, and in this area 80 % of elderly people visit their GP each year.<sup>13</sup>

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The sample drawn from the age/sex register consisted of all residents who would be 66, 71, 76, 81, or 86 years old on their next birthday, and who were alive in August 1987 (everyone aged 65, 70, 75, 80, and 85 years). Known diabetic patients were identified from the diabetes register and their records inspected to confirm the diagnosis, and to confirm that they were resident in the area when the sample was drawn.

The remainder were subjected to a modified OGTT if alive and willing. The subjects fasted overnight and then drank 388 ml of substantially degassed Lucozade, a proprietary carbonated, hydrolysed starch drink, equivalent to 75 g of anhydrous glucose. A single venous blood sample was taken 2 h later into a fluoride oxalate tube, the specimen kept cool at approximately 4°C, spun down within 4 h, and the plasma frozen for later glucose measurement on a Beckman Autoanalyser (Beckman, Fullerton, CA, USA). The results were interpreted according to 1985 WHO criteria; subjects with an initial OGTT value of 11.1 mmol l<sup>-1</sup> or more were retested within 7 days. If the second value was above 11.1 mmol l<sup>-1</sup>, the subject was diagnosed as having diabetes, and if the second value was below 11.1 mmol l<sup>-1</sup>, the subject was labelled as having Impaired Glucose Tolerance.

Those who refused the OGTT had their medical records examined for evidence of glucose tolerance status. Some subjects could not be contacted due to moving house or death, and a history was then obtained from neighbours about the subjects' fate and whether they were resident in the area when our sample was drawn. Many spouses, and some neighbours also wished to be tested, and their results were recorded separately.

If one assumes that those not tested had a similar prevalence of diabetes to those tested, then the prevalence of total diabetes (known and new) can be calculated. However, simply increasing the numbers of new diabetic subjects by the proportion not tested would give falsely precise confidence intervals; therefore, the prevalences were calculated from the actual numbers tested with a proportion of the known diabetic subjects included. Thus if number tested by OGTT =  $n$ , number not tested by OGTT =  $t$ , number of new cases of diabetes =  $d$ , and number of known cases of diabetes =  $k$ , then prevalence of new diabetes =  $d/n$ , and prevalence of known diabetes =  $k/(n+t+k)$ . The number of known cases of diabetes proportional to the number tested,  $p$ , =  $kn/(n+t)$ , and the total prevalence of diabetes =  $(d+p)/(n+p)$ .

The exact 95 % confidence intervals were calculated using the  $F$  distribution.<sup>14</sup>

## Results

Of the initial computer list of residents, 63 had died or migrated before August 1987, from 3 days to 30 years previously and included one person with known diabetes.

Of the remaining sample of 861, 48 were known to have diabetes under medical follow-up (although 15 of these were identified when offered an OGTT, rather than

from the diabetic register), and a further four subjects (aged 65, 70, 75, and 85 years) had previous plasma glucose levels diagnostic of diabetes, making 52 subjects with previously diagnosed diabetes.

Only two subjects were Asian Caucasian (one refused OGTT, one normal OGTT), and all the other 859 subjects were White Caucasian. Two subjects were residents of a convent, and five were resident in a nursing home; all these subjects received an OGTT. One subject was in geriatric continuing medical care, one in long stay psychiatric care, and one nursing home resident died. These subjects were not tested. All remaining residents (known diabetic patients, and those who were or were not tested) were resident in their own homes.

An OGTT was performed on 583 subjects. Of these 19 had diabetes, 44 had Impaired Glucose Tolerance, and 520 were not abnormal (Table 3). The acceptance rate for the OGTT fell from 80 % in the 65-year-olds to 54 % in the 85-year-olds.

The OGTT was performed on 159 spouses and neighbours aged 71 (range 65 to 85) years. Six had diabetes, and 12 had Impaired Glucose Tolerance.

## Discussion

From this sample we believe that the prevalence of previously diagnosed diabetes in Melton is 6.0 (95 % CI 4.3 to 8.1) % and the prevalence of previously undiagnosed diabetes among those not known to have diabetes is 3.3 (95 % CI 2.0 to 5.0) %. Although the spouses and neighbours were undoubtedly highly preselected, the prevalence of undiagnosed diabetes in this group was 3.8 (95 % CI 1.4 to 7.9) %, similar to the main sample.

The study area, Melton, is a Leicestershire market town which has many industries including iron and steel

Table 3. Results of diabetes screening survey in Melton Mowbray

Age/sex group	Previously diagnosed diabetes	Tested by OGTT			Not tested
		Normal	IGT	Diabetes	
65 male	3	86	9	5	21
65 female	6	112	5	2	33
70 male	7	59	3	0	24
70 female	10	65	4 (1) <sup>a</sup>	3	26
75 male	8	42	7 (1) <sup>a</sup>	1	20
75 female	9	76	5	1	36
80 male	4	23	5	3	14
80 female	2	34	0	1	25
85 male	2	5	2	0	7
85 female	1	18	4	3	20
Total	52	520	44	19	226

<sup>a</sup> Patients with initial OGTT >11.1 mmol l<sup>-1</sup> but second OGTT <11.1 mmol l<sup>-1</sup>, included in number with IGT.

works, agriculture, and pork pie, pet food, and Stilton cheese production. The elderly population is almost totally North European Caucasian. It has both rural and urban environments and a stable population. Data from the Office of Population Census and Surveys' 1971 census shows that the Standardized Mortality Ratio of the local inhabitants is 0.98 (95 % CI 0.93 to 1.04), and the age and social class structure of the population is similar to that of England and Wales (Tables 1, 2).<sup>12</sup> The socio-economic factors in the Melton area are thus similar to those of England and Wales. Although the surveys in Islington and Coventry were not so representative of the UK, their prevalence figures were both very similar to the Melton findings. It is interesting that the results of these three surveys are so similar despite differing socio-economic factors, since the prevalence of known diabetes has previously been shown to vary with these factors.<sup>15</sup>

Assuming that those subjects who were not tested had a similar prevalence of diabetes to those subjects who were tested, then the age-specific prevalences of total diabetes (known and new) can be calculated (Table 4) as described in the methods. Is this assumption valid? The NHANES 2 survey<sup>6</sup> found that those with a family history of diabetes were more likely to agree to have an OGTT and have undiagnosed diabetes, and it was thought that this increased the prevalence of new diabetes from 3.19 to 3.23 %, so participants in a study may have a higher prevalence of diabetes than the general population. The San Antonio survey<sup>16</sup> showed lower participation rates in lower socio-economic areas and the 1973 NHIS survey<sup>17</sup> found an inverse relationship between income and prevalence of known diabetes. Thus non-participants in a screening survey may have an increased prevalence of diabetes.

In the Saskatchewan Health Status Survey of the Elderly, non-respondents had significantly more numerous and longer hospital admissions than respondents<sup>18</sup> and NHANES 2 found that those not examined had more numerous hospital admissions.<sup>19</sup> Thus the diabetic subjects among this group might already be identified, reducing the number of undiagnosed diabetic subjects among the non-participants. Acceptance rates in Melton fell with age. However, in Finland<sup>6</sup> the prevalence was similar from 65 to 84 years of age, and in the Pima

Indians the prevalence was similar from 55 to 84 years.<sup>20</sup> The 1976 HIS survey had a 96 % acceptance rate and a 3.0 % prevalence of known diabetes while NHANES 2 had a 74 % acceptance rate and a 3.3 % prevalence of known diabetes. Comparison of the HIS subjects with the subjects examined in NHANES 2 reveals similar health status, hospital stays, known heart disease, known diabetes, family history of diabetes, and body mass index.<sup>19</sup> Thus it would appear that many of the factors influencing participation do not alter the prevalence of diabetes to a great extent.

The age-specific prevalence in the present study increased from 65 to 85 years of age (Table 4), but the confidence intervals are wide in the octogenarians making the significance of this uncertain.

The prevalence of diagnosed diabetes in the elderly varies from around 3 % in Southall, Poole, and Oxford, to 9 % in Leicester,<sup>1-4</sup> where it is significantly higher. This difference could be due to a genuinely higher incidence of diabetes due to a geographical cause, or to the diagnosis rate being higher in Leicester. These surveys used differing methodologies. In Southall and Oxford the inhabitants were questioned directly or by post, in Poole GP and hospital records were examined, while in Leicester the Diabetic Health Visitor records were used to identify people with known diabetes. It is the use of the Health Visitor which may explain the difference. These specialist community care Health Visitors have been informed of all newly found diabetic patients by hospital staff and GPs for the last 38 years<sup>21</sup> and visit all patients annually. Thus there is a high local awareness of diabetes, and the patients continue to be followed up, not being allowed to forget their diabetes. However, even in Melton, there were patients with previously diagnosed diabetes who had not been told the diagnosis, and neither had their health visitors.

The total prevalence of diabetes of around 8 % would suggest that many elderly diabetic patients are not diagnosed in some areas of the UK. Undiagnosed diabetes is one of the major risk factors for death from diabetic ketoacidosis.<sup>22</sup> Furthermore, it is impossible to monitor an elderly person with diabetes for eye or foot problems if the diabetes is not diagnosed.

With increasing awareness of diabetes in the elderly, and with increasingly routine blood glucose estimations, the proportion of elderly people with diabetes diagnosed would be expected to increase. This will however need an allocation or re-organization of resources if elderly diabetic patients are going to be cared for properly, particularly since the number of elderly Britons is increasing.

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Table 4. Age-specific total prevalence of diabetes in Melton Mowbray

Age (years)	Prevalence	
	%	95 % CI
65	6.3	3.5-10.3
70	10.5	6.0-16.9
75	9.7	5.4-15.7
80	11.1	4.8-21.4
85	13.8	4.6-30.4



## ORIGINAL ARTICLES

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## Fructosamine in diabetes screening of the elderly

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**SUMMARY.** The use of serum fructosamine in diabetes detection was investigated during a diabetes survey performed with a modified oral glucose tolerance test (MOGTT) on 742 residents of the Melton Mowbray area aged between 65 and 85 years. Subjects were tested in the morning and remained at rest. MOGTT results were classified by WHO criteria. The fructosamine concentration was measured in a random sub-group of 264 normal subjects and had a Gaussian distribution (mean = 1.67 mmol/L, SD = 0.126 mmol/L). In the survey as a whole 25 new diabetics were found of which 23 had fructosamine measured; 17 had values above the 95th percentile and four more had values above the 90th percentile. We have found fructosamine concentration to be a useful screen for diabetes but this may be dependent upon the standardized sampling procedure used, and the population studied.

*Additional key phrases:* population survey; modified oral glucose tolerance test; predictive values

Diabetes is defined biochemically by the blood glucose concentration, often in response to a glucose load.<sup>1</sup> Diabetes is common in the elderly, but type 2 diabetes may be asymptomatic in these subjects and it has long been realized that screening for diabetes is worthwhile.<sup>2</sup> However, even a modified oral glucose tolerance test (MOGTT)<sup>1</sup> is time consuming to organize. Although the fasting and random plasma glucose levels are easy to perform, they are insensitive<sup>3,4</sup> compared to a glucose tolerance test.

Several population based studies have examined the use of glycosylated haemoglobin levels for this screening purpose,<sup>3,5</sup> but found them to be of limited value. It has been suggested that fructosamine may be better than glycosylated haemoglobin for screening,<sup>6</sup> but another study found the glycosylated haemoglobin superior.<sup>7</sup> However, most studies investigating the use of fructosamine for screening have been marred by poor subject selection for the non-diabetic control group, and/or have not been based on the general population.<sup>6-10</sup> One population survey omitted to screen for undiagnosed diabetic subjects.<sup>11</sup>

Since fructosamine is cheap and relatively simple to measure, we investigated its use whilst screening the elderly of Melton Mowbray for

diabetes. Details of this survey have been described previously.<sup>12</sup>

### SUBJECTS AND METHODS

A sample comprising of all elderly people aged 65, 70, 75, 80 and 85 years old resident in Melton Mowbray and environs was drawn from a computerized population age/sex register. Known diabetics were identified from the local diabetic register, and excluded; the remainder had a MOGTT, if alive and willing. Spouses of the subjects were also offered a MOGTT, if over 65 and their results are included with those of the main sample.

The MOGTT was performed according to WHO criteria; after an overnight fast, the subjects drank 388 mL of Lucozade which contains the equivalent of 75 g anhydrous glucose in the form of hydrolysed starch. The subjects rested until a venous blood sample was taken 2 h later for plasma glucose and serum albumin and fructosamine measurements. The blood samples were kept at 4 °C, separated within 4 h, and the plasma and serum frozen for later analysis.

The subjects also collected a random urine sample which was tested using BM-test-5L strips for glycosuria (Boehringer Mannheim, Sussex, UK).

Plasma glucose was measured on all subjects using the glucose oxidase method on a Beckman

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TABLE 1. The normal fructosamine distribution and the distribution of subjects with abnormal glucose tolerance

	Percentiles for normal glucose tolerance subjects					
	70	80	90	92	95	99
Normal subject's fructosamine (mmol/L)	1.73	1.76	1.82	1.86	1.92	2.15
Diabetics with fructosamine above percentile (number)	21	21	21	20	17	13
Sensitivity (%)	91	91	91	87	74	57
Predictive values of fructosamine for diabetes (%):						
Positive	8.5	12	20.8	23.5	30.9	66.3
Negative	99.6	99.6	99.7	99.5	99.1	98.6
IGT subjects with fructosamine above percentile (number)	27	22	14	12	5	0

glucose analyser 2 (Beckman Instruments, Galway, Eire).

The results of the MOGTT were interpreted according to 1985 WHO criteria;<sup>1</sup> if a 2 h glucose concentration was 11.1 mmol/L or more, a second MOGTT was performed within 7 days. If the second result was 11.1 mmol/L or more, the subject was labelled diabetic, but if less than 11.1 mmol/L the subject was labelled as having Impaired Glucose Tolerance (IGT).

Serum fructosamine was measured on a random selection of subjects with normal glucose tolerance and on most subjects with an abnormality of glucose tolerance, using the method of Johnson *et al.*<sup>13</sup> on a Cobas Bio centrifugal analyser (Roche Products Ltd, Welwyn Garden City, UK). The reagent was prepared in-house and comprised 0.1 mmol/L sodium carbonate buffer (pH 10.35 at 20 °C containing 0.25 mmol/L nitro blue tetrazolium). The calibration material was a glycated albumin pool, standardized against an aqueous solution of 1-deoxy-1-morpholinofructose which contained 40 g/L human albumin. The within batch coefficient of variation (CV) was 1.2% (mean 1.69 mmol/L) and between batch CV was 2.2% (mean 1.22 mmol/L).

Serum albumin was measured in these subjects using the bromocresol green method on a Technicon SMACII analyser (Technicon Instruments, Basingstoke, UK).

## RESULTS

In the survey as a whole 742 residents were tested, 25 new diabetics were found and 56 people had IGT. The serum fructosamine concentration in 264 subjects with normal glucose tolerance had a Gaussian distribution, with a mean of 1.67 mmol/L and standard deviation of 0.126 mmol/L. There was no sex difference in fructosamine level in normal subjects (women mean = 1.672 mmol/L, SD = 0.0130; men

mean = 1.664 mmol/L, SD = 0.122; *t* test  $P > 0.1$ ), and age also had no effect (correlation coefficient = -0.182; deviation from nil correlation  $t = 2.99$ ,  $P > 0.1$ ).

The serum fructosamine concentration was measured in 23 previously undiagnosed diabetic subjects (median = 2.15 mmol/L; range = 1.6 to 3.45 mmol/L) and in 48 subjects with IGT (median = 1.74 mmol/L; range = 1.4 to 2.13 mmol/L).

The percentile distribution of fructosamine concentrations in normal subjects is given in Table 1, together with the distribution of values from the subjects with abnormal glucose tolerance; two diabetic subjects had fructosamine levels below the 70th percentile (1.60 and 1.67 mmol/L). By extrapolating from the 264 normal subjects to all 661 normal subjects, and including IGT subjects, the predictive values of the fructosamine level to distinguish from diabetic and non-diabetic subjects were calculated.

The IGT group included three subjects who had an initial MOGTT result greater than 11.0 mmol/L but were classified as IGT after second MOGTT; their fructosamine concentrations were 1.73, 1.89, 1.95 mmol/L.

All patients had albumin levels within the normal range (35–55 g/L), 13 of the 23 diabetics had glycosuria (tested with BM-test-5L strips).

## DISCUSSION

These results show that using the 95th percentile (1.92 mmol/L) as a cut-off point, fructosamine achieves a sensitivity of 74% in detecting diabetic subjects and if the 90th percentile (1.82 mmol/L) is used the sensitivity is 91%. The results from this study show a better performance than two other studies<sup>6,9</sup> which preselected subjects, thus improving the performance of their test. Two previous studies used fructosamine in population based screening surveys; one found less sensitive results in elderly Dutch with a sensitivity of 47%

at a specificity of 92%<sup>14</sup>, whereas a corresponding sensitivity of 87% was found in our study. On examining Moslem Asians in Tanzania, a sensitivity of 19% at a specificity of 99%<sup>15</sup> was found.

Several factors improved the discriminatory power of serum fructosamine in our study. The tests were done in the morning, minimizing diurnal variation and the subjects rested during the MOGTT reducing variations in fructosamine level due to posture and activity,<sup>16</sup> none of the subjects had an acute illness and all had a normal serum albumin. Although age *per se* does not effect glycosylation of other tissues proteins,<sup>17</sup> our normal was defined for a specific sector of the population (elderly British Europeans), which may also have helped.

In this study the diagnosis was confirmed by a repeat MOGTT reclassifying three subjects as IGT who would have been labelled as diabetic otherwise. If these three subjects are classified as diabetic, it reduces the sensitivity of the fructosamine test slightly (95th percentile sensitivity 66.7%; 90th percentile sensitivity 85%); this may be a factor in the lower sensitivity of other studies.

However, many of these discriminatory factors also applied to the study in Tanzania,<sup>15</sup> which showed considerable overlap between normal and diabetic fructosamine values. The Tanzanian study included subjects of all age groups; the normal range was derived from half the normal subjects in each age group which would introduce a bias towards young subjects, whilst one would expect diabetes to be commoner in older subjects. Of Tanzanians tested 23% had IGT and fructosamine levels overlapped considerably with those of normal and diabetic subjects, thus reducing the predictive value of the test. However, only six of the 32 new diabetic Tanzanians had an elevated fructosamine which suggested that non-diabetic Tanzanians have higher blood glucose levels than subjects from areas with a low prevalence of glucose intolerance.

Thus we have found that the fructosamine concentration is a reasonable tool for detecting diabetes but this depends not only on the survey method, but also on the study population. It is particularly important to define the normal range for the study population since the normal upper limit for serum fructosamine level varies greatly from 1.18 mmol/L in Tanzania,<sup>15</sup> to 3.12 mmol/L in Kawerau.<sup>11</sup> Because of the way diabetes is presently defined, fructosamine

does not replace the glucose tolerance test (GTT), although some would argue that the GTT itself is not a particularly good test.<sup>18</sup> The fructosamine level could prove useful as a simple screen for subjects at risk of being diabetic to select a sub-group in whom a GTT would be worthwhile.

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## The Mortality of Elderly People with Diabetes

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To assess the full effect of diabetes on survival in elderly subjects, residents of Melton Mowbray aged 65, 70, 75, 80, and 85 years were screened by glucose tolerance test and followed up for 4.5 years. Death occurred in 56 of 520 normal subjects, 9 of 44 subjects with impaired glucose tolerance, 7 of 19 newly diagnosed diabetic subjects, and 27 of 52 known diabetic subjects. Diabetic subjects were 4.5 times (95% confidence interval 2.9–7.0) more likely to die than subjects with normal glucose tolerance. Thus elderly diabetic subjects have a substantially increased risk of death compared to their normal glucose tolerant peers.

**KEY WORDS** Diabetes mellitus Elderly subjects Mortality

### Introduction

The effect of diabetes on mortality in the elderly is controversial but is generally assumed to be minimal, particularly in subjects over 75 years of age.<sup>1,2</sup> Wong *et al.*<sup>3</sup> have reported that in a population of known diabetic subjects, the standardized mortality ratio of subjects 75 years or older was significantly lower than the general population at 88%. Waugh *et al.*<sup>4</sup> reported, also in a population of known diabetic subjects, that the relative risk of death in diabetic subjects aged 75 or over was slightly higher than in the general population at 130%. Neither of these studies screened the population using a glucose tolerance test (GTT). Most studies on mortality in the elderly diabetic subject examine the effect only in those subjects whose diabetes is known;<sup>1</sup> since many elderly diabetic subjects remain undiagnosed, the full impact of mortality associated with diabetes may be underestimated, particularly since subjects with impaired glucose tolerance (IGT) and diabetes found in the Bedford screening survey had higher subsequent mortality than those subjects found to have normal glucose tolerance.<sup>5</sup> The elderly of Melton Mowbray were previously screened for diabetes<sup>6</sup> using a GTT. This was repeated if abnormal, fulfilling strict WHO criteria.<sup>7</sup> The aim of this study was to examine their subsequent mortality.

### Patients and Methods

As described previously,<sup>6</sup> Melton Mowbray is ideal for epidemiological research, it is a market town in the Midlands with age, sex, and social class similar to the UK average, and all residents attend one general practice which, in conjunction with the Leicester University

epidemiology department, maintains an accurate computerized population register.

All subjects on the register aged 65, 70, 75, 80 or 85 years on 1 August 1987 were studied.<sup>6</sup> Known diabetic subjects were identified from the diabetes register, while the remainder underwent a modified oral GTT if alive and willing. Venous plasma glucose levels (glucose oxidase method) were measured 2 h after 75 g oral anhydrous glucose. The results were interpreted according to the 1985 WHO criteria;<sup>7</sup> if the glucose level was greater than 11.1 mmol l<sup>-1</sup>, the test was repeated within 7 days.

Subjects were registered with the National Health Service Central Registry who upon death returned copies of death certificates. Details of deaths were also obtained from the Leicestershire mortality list; this register is compiled by Leicestershire District Health Authority and the Leicester University epidemiology department from death certificates of all Leicestershire residents.

Survival was calculated from the start of the study (1.8.87) for known diabetic subjects or from the date of the GTT, or the date of refusal for other subjects. Analysis was performed using Cox's proportional hazards regression model, with age group and sex as defining strata. The study was approved by the Leicestershire Health Authority.

### Results

From the Melton general practice register there were 861 subjects in the specified age ranges: 52 were known diabetic subjects and 191 refused testing. Glucose tolerance testing revealed 19 previously undiagnosed diabetic subjects, 44 had IGT and 520 had normal glucose tolerance. The other 35 had either died or left the area before being asked to participate in the study. The age and sex distribution of the groups are shown in Table 1.

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Table 1. Age and sex distribution of cohort

Age/Sex	Known diabetes	Diabetes	Tested by GTT IGT	Normal	Refused GTT
65/Male	3 (1)	5 (3)	9 (0)	86 (6)	18 (4)
65/Female	6 (2)	2 (1)	5 (2)	112 (7)	30 (2)
70/Male	7 (4)	0 (0)	3 (1)	59 (5)	23 (2)
70/Female	10 (3)	3 (0)	4 (0)	65 (3)	24 (2)
75/Male	8 (6)	1 (0)	7 (1)	42 (6)	16 (2)
75/Female	9 (5)	1 (0)	5 (0)	76 (6)	33 (5)
80/Male	4 (3)	3 (2)	5 (2)	23 (5)	9 (3)
80/Female	2 (1)	1 (0)	0 (0)	34 (8)	17 (6)
85/Male	2 (2)	0 (0)	2 (2)	5 (1)	4 (4)
85/Female	1 (0)	3 (1)	4 (1)	18 (9)	17 (6)
Total	53 (27)	19 (7)	44 (9)	520 (56)	191 (36)

Numbers in parentheses are number dead within 4.5 years.

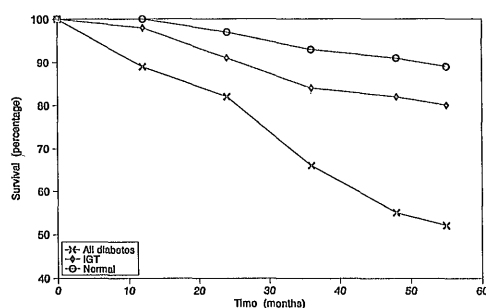


Figure 1. Survival of subjects

Up to January 1992 death had occurred in 56 (11%) of normal subjects, 27 (52%) of the known diabetic subjects, 7 (37%) of the discovered diabetic subjects, 9 (20%) of the subjects with IGT, and 34 (18%) of those who refused testing. Survival curves of each group (unadjusted for age and sex) are shown in Figure 1.

All GTTs were performed in ostensibly fit subjects and the first death in the newly diagnosed diabetic group occurred thirteen months after GTT.

The principal causes of death given on the death certificates are given in Table 2. There was an excess of vascular (cardiovascular, cerebrovascular, peripheral vascular, and ischaemic bowel combined) deaths among

Table 2. Distribution of principal causes of death on the death certificate

Subjects (number)	Cause of death (numbers)		
	Vascular	Neoplastic	Other
Normal (56)	32	15	9
Diabetic (34)	24	5	5
IGT (9)	5	1	3

the diabetic subjects but this was not significant. Diabetes appeared on the death certificates of 2/7 newly diagnosed and 12/27 known diabetic subjects.

The relative risk (95% confidence intervals) of death after adjustment by age and sex, compared with the normal glucose tolerant subjects was 4.5 (2.9–7.0) in all diabetic subjects (i.e. known and newly diagnosed combined), 5.2 (3.2–8.5) in known diabetic subjects, 3.0 (1.3–6.6) in discovered diabetic subjects, 1.7 (0.8–3.5) in subjects with IGT and 1.5 (1.0–2.4) in those who refused testing.

The relative risk of death of the known diabetic subject compared with the discovered diabetic subject was 1.1 (1.2–2.6).

Comparison of all diabetic subjects versus normal subjects for individual age groups is given in Table 3.

## Discussion

The results of this study suggest that in the elderly both known diabetes and diabetes discovered by screening are associated with a substantially increased mortality. Because the numbers of subjects, particularly in the diabetic groups, are small, the relative risks of death have wide confidence intervals but from the ages of 6 to 75 the lower confidence interval is greater than 1.0. Because of the long interval between testing and death it is likely that the subjects had diabetes rather than abnormal glucose tolerance related to illness.

Previous studies have suggested diabetes is associated with increased mortality but that above the age of 75 mortality is only slightly increased<sup>4</sup> or is significantly reduced in diabetic subjects.<sup>3</sup> In these studies, however, the population was not screened and a cohort of known diabetic subjects was compared with the general population which undoubtedly included unrecognized diabetic subjects. The present study is probably a more accurate reflection of the effect of glucose tolerance on mortality as only groups whose glucose tolerance was determined by GTT were compared; diabetes was associated with a marked increase in risk of death at 75, but in octogenarians the lower confidence interval (CI) were below 1.0, possibly due to the limited number of subjects.

Stengård *et al.* reported on the subsequent mortality

Table 3. Relative risk of death for all diabetic subjects compared to normal subjects for individual groups

Age	Relative risk of death (95% CI)
65	12.1 (3.5–41.81)
70	4.7 (1.4–16.36)
75	7.0 (3.0–16.2)
80	2.5 (0.8–7.9)
85	1.3 (0.4–5.0)

of elderly men screened by GTT in eastern and western Finland;<sup>9</sup> they found that the risk of death compared to normal subjects over 5 years was 2.33 times for diabetic men aged 65 to 74 years and 1.84 for diabetic men aged 75 to 84 years. Although the Finnish results suggest a lower mortality, the 95% CI for the two surveys overlap; also, it has been previously noted<sup>9</sup> that this Finnish screening study suffered methodological problems which tended to double the number of subjects with an abnormal GTT result; thus, the diabetic patients found in the Finnish study may not have been diabetic if tested in the morning after a 9 h fast, and inclusion of subjects without diabetes in the diabetic group would tend to decrease the mortality in the diabetic group.

Although the mortality of those that refused the GTT was slightly higher than the mortality of normal subjects, the lower 95% CI did reach 1.0, the comparison of refusing subjects to all subjects tested (i.e. normal, IGT, and new diabetic subjects) revealed no significant difference ( $p=0.75$ ). In the original description of the Melton diabetes survey,<sup>6</sup> it was felt that non-recruitment related to age probably did not bias the results significantly; the similar mortality would be further evidence to suggest that glucose tolerance status was similar in those that accepted and those that refused a GTT.

The results of this study suggest that previously undiagnosed diabetes detected by screening is associated with substantially increased mortality. There are no trials of early treatment of diabetes detected by routine screening to see if this reduces mortality, but our results suggest that this would be appropriate. However, it is known that good care improves survival<sup>10</sup> of subjects with Type 2 diabetes and this study provides further evidence of the need for high quality care of the elderly diabetic subject.

#### Acknowledgements

We are grateful for the help of M. Bodington, J. Botha, and the residents and medical practitioners of Melton Mowbray.

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# Care of the Elderly Person with Diabetes: A Questionnaire Study Comparing Geriatricians with Diabetic Specialists

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## Summary

The management of elderly diabetic patients by 100 geriatricians and 100 diabetologists was assessed by a postal questionnaire. Replies were initially received from 54 geriatricians and 81 diabetologists ( $p < 0.001$ ); geriatricians were re-contacted increasing replies to 71. The geriatricians were less likely to check the visual acuities ( $p < 0.001$ ), less likely to dilate the pupils for fundoscopy ( $p < 0.025$ ), less likely to refer a patient with maculopathy to an ophthalmologist ( $p < 0.001$ ), more likely to discharge a stable diabetic to general-practitioner care ( $p < 0.05$ ), less likely to use insulin ( $p < 0.01$ ) or antidepressants ( $p < 0.01$ ) in treating painful peripheral neuropathy, and more likely to use glibenclamide instead of a shorter-acting sulphonylurea ( $p < 0.001$ ).

## Introduction

Diabetes mellitus is a common disease of the elderly, and geriatricians are taking a larger role in medical care. It is interesting, therefore, to discover whether the diabetic care of the geriatricians differs from that of physicians with special training and experience in the management of diabetic patients.

## Method

One hundred acute hospitals were randomly selected from the *Medical Directory* [1]. Their geriatricians were identified by job title and specialists in diabetes were identified by either being in charge of the diabetic clinic or by membership of the British Diabetic Association. All were sent a questionnaire on the management of three diabetic case histories.

*Case 1:* a 68-year-old lady (height 168 cm weight 70.7 kg) presents with asymptomatic glycosuria and a random blood sugar of 14.4 mmol/l. She takes

bendrofluazide 10 mg daily for hypertension: history otherwise unremarkable.

*Case 2:* a 69-year-old man (height 178 cm, weight 71.6 kg) has been diabetic for 10 years controlled on diet alone. His weight is normally 75.6 kg; he complains of pains in his feet at night. Examination revealed foot pulses present, absent ankle jerks, vibration sense absent below iliac crests and his soles were tender to touch. Investigations showed a glycosylated haemoglobin of 10.8% (4–8.5%) and random blood sugar of 15 mmol/l.

*Case 3:* a 70-year-old lady with type 2 diabetes complains of poor vision. Her optician reported that 1 year previously her visual acuity (V.A.) was 6/6 both eyes, but is now reduced to 6/12 and 6/9; there are no cataracts but there are 'changes at the back of the eye'. Fundoscopy revealed hard exudates above and lateral to the macula in the right eye (V.A. 6/9) and background changes but macula apparently normal in the left eye (V.A. 6/12).

Doctors were also asked which sulphonylurea they would use in patients aged over 70. In view of the low (54%) response rate from the initial mailing, the geriatricians were re-contacted.



Results were analysed by the  $\chi^2$  test with Yates's correction.

### Results

Of the 100 questionnaires in each group, we received replies from 54 geriatricians and 81 diabetes specialists, a significant difference in response rate ( $p < 0.001$ ). Re-contacting the

geriatricians produced three duplicate replies, two that had not received the initial posting, and 15 new replies. The first and second letters to geriatricians produced replies with no statistically significant differences, and the two sets of responses were analysed together.

The replies on case histories 1-3 are given in Tables I-III, respectively. The choice of sulphonylurea (Table IV) was varied, but the main

Table I. Management of a newly-found diabetic

Would you?	p	Number answering yes	
		Diabetologists (n = 81)	Geriatricians (n = 71)
Measure visual acuity	****	60	27
Perform fundoscopy		80	69
Dilate the pupils	****	63	27
Measure BP sitting	****	38	52
Measure BP lying		72	66
Examine vibration sense at the ankles	****	75	50
Examine the peripheral pulses		80	69
Measure the glycosylated haemoglobin		40	37
Measure the creatinine $\pm$ L.F.T.s		68	58
Treat with diet alone†		18	12
Treat with oral hypoglycaemics		1	4
Treat with diet and change antihypertensive		61	55
When stable, discharge to GP	*	45	52

\*  $p < 0.05$ , \*\*  $p < 0.025$ , \*\*\*  $p < 0.01$ , \*\*\*\*  $p < 0.001$ .

† One diabetic specialist wanted confirmation of her diabetes and thus did not treat her.

Table II. Management of painful peripheral neuropathy

	p	Number of diabetologists (n = 81)	Number of geriatricians (n = 71)
Would treat the patient with insulin	***	50	25
Would use paracetamol	**	14	25
Would use antidepressants	***	33	14
Would use anticonvulsants		22	21

\*  $p < 0.05$ , \*\*  $p < 0.025$ , \*\*\*  $p < 0.01$ , \*\*\*\*  $p < 0.001$ .

Table III. Management of patient with probable maculopathy

	p	Number of diabetologists (n = 81)	Number of geriatricians (n = 71)
Would dilate the pupils	**	72	51
Would refer to ophthalmologist	****	74	49
Would not dilate eye or refer on		0	4

\*  $p < 0.05$ , \*\*  $p < 0.025$ , \*\*\*  $p < 0.01$ , \*\*\*\*  $p < 0.001$ .

Table IV. The choice of sulphonylurea

	p	Number of diabetologists (n = 81)	Number of geriatricians (n = 71)
Tolbutamide	***	30	10
Glibenclamide	****	13	33
Glipizide		7	8
Gliclazide		10	2
Chlorpropamide		2	0
Gliquidone		0	2
Several including glibenclamide†		4	12
Several not inc. glibenclamide		15	1
'None', 'short-acting', metformin		0	3

\*  $p < 0.05$ , \*\*  $p < 0.25$ , \*\*\*  $p < 0.01$ , \*\*\*\*  $p < 0.001$ .

† Some replies consisted of a short list of sulphonylureas.

difference was the use of glibenclamide by only 17 diabetologists compared with 45 geriatricians ( $p < 0.001$ ).

### Discussion

The first case represented a patient with a common problem, i.e. an overweight, probable type 2 diabetic on a thiazide diuretic. The exact criteria for the diagnosis of diabetes has not been met, since she was asymptomatic; the other feature of note was her diuretic which may have provoked her diabetes. The two groups were just as likely to measure the liver function and creatinine which would have been necess-

ary later if metformin or a sulphonylurea were used [2]. The two groups would measure the glycosylated haemoglobin equally frequently; treatment in the form of diet and changing the thiazide was an easy first step, and therefore the HbA1 was an unnecessary expense. Seventy-six per cent would treat the lady with a diet and change or review antihypertensive medication, which follows the consensus view that diet should be tried first [3, 4]. Four geriatricians would initiate oral hypoglycaemics before a trial of diet, but this was not significant ( $p > 0.05$ ).

Once the patient was controlled, the diabetologist was more likely to follow her up and the geriatrician was more likely to discharge her ( $p < 0.05$ ). Discharge to general practitioners

(GPs) may be harmful for diabetics [5, 6], but GP mini-clinics may perform as well as hospital clinics [7]; there are very many elderly diabetics, often with transport difficulties, and thus discharge to enthusiastic GPs with mini-clinics is reasonable.

Geriatricians and diabetic specialists looked at the optic fundus equally frequently, but differed in their method of assessment. The geriatrician was less likely to dilate the pupils or measure the visual acuity ( $p < 0.001$ ) compared with the diabetologist. These techniques [8, 9] are recommended because the elderly diabetic patient commonly has retinopathy at presentation [10].

The third patient (Table III) probably has maculopathy. Mydriasis and visual acuity measurement are necessary to detect early macular disease; photo-coagulation preserves vision, but only if the acuity is 6/12 or better [11, 12]. The geriatrician was less likely to dilate the pupils ( $p < 0.025$ ) and less likely to refer the patient to an ophthalmologist ( $p < 0.001$ ).

Patient number two (Table II), an elderly man with painful peripheral neuropathy, weight loss and poor diabetic control represents diabetic neuropathic cachexia [13]. The recommended treatment is insulin [14, 15]; 35% of geriatricians would use it compared to 62% of diabetologists ( $p < 0.01$ ). Treatment of the pain of diabetic neuropathy is difficult, but the consensus view is that tricyclic antidepressants are probably best after strict metabolic control [16]. The geriatrician was more likely to use paracetamol ( $p < 0.025$ ) and was less likely to use tricyclics ( $p < 0.01$ ) than the diabetologist. However, paracetamol is safer than the tricyclics in elderly patients, and is probably worth an initial trial.

There was a marked difference in favoured sulphonylurea (Table IV) with the diabetic specialists preferring a short-acting agent such as tolbutamide, and the geriatricians preferring glibenclamide ( $p < 0.001$ ), often for reasons of compliance. However, even 2.5 mg of glibenclamide has caused fatal hypoglycaemia [17], occurring up to 72 h after the last dose [18, 19]. Thus, recent reviews recommend the short-acting sulphonylureas [3, 4]; hypoglycaemic reactions have occurred on these also, stressing

the need to be certain that they are necessary [20].

In summary, there was of course much similarity between the two groups of physicians regarding the management of the elderly diabetic patient, but there were particular differences on eye problems, treatment of painful diabetic neuropathy, and use of oral hypoglycaemic agents. This difference might simply be due to increased specialist knowledge by the diabetologist. However, we also feel that the full significance of the early diabetic is underestimated in terms of both numbers and morbidity. The prevalence of diabetes in the elderly population is about 9% [21]; the elderly diabetic has a higher risk of blindness from maculopathy [12] and has a higher risk of amputation than younger diabetics or his non-diabetic peers [22]. Despite this, we believe that some geriatricians still equate non-insulin-dependent diabetes with 'mild' diabetes.

#### Acknowledgements

We are grateful to all who completed the questionnaires (copies available on request), and to M. L. Burden and M. Bodington for all the clerical work.

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## Letters to the Editor

### Care of the Elderly Person with Diabetes: completing the Audit Cycle

SIR—In 1988 the geriatricians' and diabetologists' management of elderly diabetic subjects was compared [1] revealing that geriatricians were using more glibenclamide and were not dilating pupils for fundoscopy; not surprisingly, they were less expert on specialized topics e.g. diabetic neuropathic cachexia.

The study was presented at the 1989 spring BGS meeting; since then, relevant information has appeared in *Drugs and Therapeutics Bulletin*, *Geriatric Medicine*, and *Care of the Elderly*; a BGS diabetic special-interest group now exists.

Has the management of the elderly diabetic improved? As in the original study [1], questionnaires were randomly sent to 100 geriatricians and 100 diabetologists. Only three questions were asked:

1. Which sulphonylurea would you use in the elderly?
2. Would you routinely dilate the pupils of a new diabetic subject?
3. Would you discharge a stable diabetic to his/her GP?

Results were compared with those of 1988 (Table) using Fisher's exact test (two-tailed).

In 1988, the geriatricians' initial response rate was

54%; in 1992 this rate had increased to 69% ( $p=0.041$ ), due to either greater interest, or shorter questionnaire.

The geriatricians' choice of sulphonylurea has swung dramatically from glibenclamide to the shorter-acting agents, tolbutamide, gliclazide and glipizide, over the last 4 years ( $p<0.001$ ) and now resembles the use of shorter-acting agents by diabetologists in 1988 ( $p=0.14$ ). From 1988 to 1992 the diabetologists used even less glibenclamide ( $p=0.0004$ ), and still use less than today's geriatricians ( $p=0.038$ ). Avoidance of glibenclamide is now recommended in the *British National Formulary* [2]. A new problem is that glipizide, used by 15 diabetologists and 12 geriatricians, is far more likely to cause hypoglycaemia in the elderly than the young, despite being short acting [3].

The geriatricians' rate of mydriatic use has remained static ( $p=0.39$ ) and is still less than the diabetologists' use in both surveys ( $p<0.0001$ ).

Originally, the geriatrician was more likely than the diabetologist to discharge a stable diabetic to the GP, but the geriatrician is now less likely to discharge than in 1988 ( $p=0.034$ ), with a similar rate to the diabetologists of 1988 and 1992 ( $p>0.5$ ). The diabetologists' discharge practice has not changed ( $p=0.27$ ).

Thus the geriatricians have improved their care of the elderly diabetic patient over the last 4 years by avoiding glibenclamide; they may also be more interested in the problem since the response rate was greater and they were less likely to discharge the patient to the GP. However, they are still not routinely dilating pupils for fundoscopy despite its recommendation [4].

We are grateful to everyone who has returned questionnaires; reprints of the original study are available from S.C.M.C.

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<sup>a, b</sup> A further 2 and 1 diabetologists, respectively, would use chlorpropamide.

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#### Assessment for Nursing Homes in Scotland

SIR—The article by MacPherson, Donald and Ludbrook on assessment for private nursing homes in Scotland [1] fundamentally misses the point concerning the use of the word 'assessment'. The authors judge assessment solely on whether it is practised, but not upon its purpose, and they conclude that physicians must adjust their viewpoint. However, they fail to consider that diagnostic, rehabilitative and multidisciplinary management is inherent in the geriatric medical literature in the use of the word assessment. Thus their conclusions, though of interest, are invalid. The question still remains: would it be preferable for all patients referred to long-stay hospitals, residential and nursing homes, to have prior multidisciplinary assessment by physicians and their teams skilled in geriatric medicine?

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1. MacPherson I, Donald S, Ludbrook A. Registered private nursing homes in Scotland: referral and assessment practice. *Age Ageing* 1992;21:429-34.

The above letter was referred to Dr MacPherson and colleagues who offer the following reply:

SIR—Professor Millard is correct to draw attention to a lamentable lack of evidence as to the workings of assessment in practice. We agree that one cannot equate quantity to quality in this area and it was never our intention to do so. However, what we did try to draw attention to was the composition of the assessment and the modes of interpretation of the assessment data were mirrored in the research findings from other care sectors and thus the nursing-home sector (certainly in Scotland) was not in that sense

'deviant' as was being suggested by previous commentators.

No-one would dispute the special skills of the geriatrician, and certainly we would never argue against their involvement in the assessment process; the question is whether only the geriatricians and their teams should be involved. Some commentators have taken this line arguing on grounds of experience and consistency. To take the latter point first, we drew attention to the fact that clinicians can be as variable in their assessments as any other profession and therefore that is not in itself a strong argument for their primacy. Taking the former point, the geriatrician's experience is in assessing primarily for different types of 'hospital' care versus residential and domiciliary care. Images are built of what is and is not feasible from the point of view of the patient and the prospective recipient service. What we have tried to point to is that we are still trying to determine the place of the nursing home in the care spectrum but that the available research suggests the operational philosophy is closer to residential care. Therefore clinicians must take on board 'suitability' for the individual nursing home as a key criterion in assessing for nursing-home care, as some already do in connection with local authority residential care. That is the adjustment we argue for.

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#### Long-term Outcome following Stroke

SIR—Greveson *et al.* [1] made no mention of incontinence in their study on the long-term outcome for patients and carers following stroke.

There is no doubt that incontinence associated with a stroke is a bad prognostic feature. Wade and Hewer [2] suggested that urinary incontinence was more specific and had a higher predictive value than impairment of consciousness when considering the outcome of stroke. Brocklehurst *et al.* [3] found a good correlation with urinary incontinence and ADL function. Borrie *et al.* [4] reported that incontinence at 4 weeks was associated with a moderate or severe motor defect, impaired mobility and mental impairment. Barer [5] showed that the severity of incontinence was correlated with death rate, discharge home rate (for which it was a more powerful predictor than the severity of hemiparesis), recovery of limb strength and independence in ADL.

Since it is well known that incontinence *per se* is