STUDIES OF METABOLIC CONTROL AND COMPLICATIONS IN INSULIN DEPENDENT DIABETES MELLITUS

2 VOLUMES

VOLUME II

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CHAPTER 3

THE SALFORD HOME BLOOD GLUCOSE MONITORING PROJECT - RESULTS

RESULTS FROM THE SALFORD HOME BLOOD GLUCOSE MONITORING PROJECT

In a study of this scale some data is inevitably missing or unreported. In some cases this is an aspect of assessment in the study, e.g. in assessing compliance by the number of appropriately collected blood spot filter paper cards returned during the study. Consequently for each of the results sections I will state at the beginning whether or not subgroup analysis was performed deliberately or whether data was incomplete.

1:1 PATIENT RECRUITMENT AND DROP OUT RATES

450 - 500 insulin-treated diabetics could initially have been considered for the study, of whom roughly 300 would have fulfilled most of the entry criteria. During the 18 month recruitment period over 200 patients were approached of whom 153 agreed to participate in the study. Their progress and the drop outs are recorded in Table 19.

Over 50% of insulin-dependent diabetics who were subsequently identified as suitable for the study were recruited initially. This pick up rate is high enough to minimise any selection bias. Of 153 patients, 124 completed 1 year of the study. The 19% drop out rate is roughly that expected in such studies, and is low enough to allow sequential analysis by groups. In the second year of the study the drop out rate was even lower so that of 124 patients 123 completed the study. The 2 deaths in the run in period were due to myocardial infarction and of the two who died following randomisation, one developed bowel cancer to which he succumbed, and the other died

Table 19. PATIENT RECRUITMENT AND DROP-OUT RATE IN THE HOME BLOOD GLUCOSE MONITORING STUDY.

No. OF INSULIN-TREATED DIABETICS IN SALFORD IDENTIFIED FOR U100 CHANGEOVER			Approx.500
No. AVAILABLE AND SUITABLE FOR THE HOME BLOOD GLUCOSE MONITORING STUDY			Approx.300
No. INTERVIEWED REGARDING PARTICIPATION IN THE STUDY			200
No. WHO ENTERED INITIAL RUN-IN (INTENSIVE) PHASE I OF STUDY			153
WITHDRAWAL DURING RUN-IN PHASE OF STUDY		-6	
DEATHS DURING RUN-IN PHASE	2		
NON-COMPLIANCE WITH STUDY PROTOCOL (NON-ATTENDANCE)	4		
No. SUITABLE FOR RANDOMISATION (PHASE 2)			147
WITHDRAWAL AT POINT OF RANDOMISATION		-18	
REFUSAL TO GIVE UP BLOOD GLUCOSE METER WHEN RANDOMISED TO URINE TESTING	2		
"INSUFFICIENT TIME FOR STUDY"	5		
"ANXIETY"	1		
INABILITY TO COMPREHEND	2		
FAILURE TO ATTEND	3		
DEATH	2		
"SOCIAL PROBLEMS"	2		
LEFT AREA	1		
No. WHO COMMENCED PHASE 2 (BLOOD vs URINE TESTING) OF STUDY			129
DROP-OUTS DURING 1st YEAR OF STUDY		-5	
DEATHS	2		
AMPUTATION OF LIMB	1		
NON ATTENDANCE	1		
LEFT AREA	1		
No. WHO COMPLETED 1st YEAR OF STUDY			124
No. WHO COMMENCED PHASE 3 (YEAR 2) OF STUDY			124
DROP-OUTS DURING 2nd YEAR OF STUDY		-1	
No. WHO COMPLETED 2nd YEAR OF STUDY			123

from cardiac failure secondary to myocardial infarction. 60% of the patients had no relevant past medical history. Coronary heart disease was previously documented in 3 (2%) patients, hypertension in 4 (3%), peripheral vascular disease in 3 (2%), chronic obstructive airways disease or asthma in 22 (14%), associated endocrine disease (predominantly thyroid disease) in 9 (6%), articular disease in 10 (7%), early renal disease in 3 (2%), pancreatic disease in 3 (2%) and hyperlipidaemia in 1 (0.7%).

40% of patient were on regular medication at entry to the trial, primarily analgesics (10%), hypnotics (8%), non-steroidal anti-inflammatories (5%), thyroxine (4%), antibiotics (4%), bronchodilators (3%), peripheral vasodilators (3%), β Blockers (3%), antidepresants (3%),diuretics (2%), haematinics (2%), antacids/H_2 antagonists (2%) and lipid lowering agents (0.7%). 6 women were on the oral contraceptive at entry to the study. No patients were on anticoagulants, digoxin, antiplatelet agents, calcium antagonists or ACE inhibitors. Of the original 153 patients, 98 were working at entry to the study. Of these, 72 (73%) had not missed any time from work in the preceding year. In the remaining 26 patients, the duration of time off work ranged from 1 - 25 days, with a mean of 7.5 days.

1:2. RANDOMISATION TO BLOOD OR URINE GLUCOSE TESTING

Of the 147 individuals suitable for randomisation to either blood or urine glucose testing, 68 were allocated blood glucose testing and 79 were allocated to urine glucose testing. This inequality of numbers reflects the 20 block randomisation

schedule. In the event, of the 124 patients who completed 1 year in the study, roughly equal numbers were performing either blood (61) or urine (63) testing. The characteristics of the 153 patients who started the study are compared with these randomised to blood or urine testing and the control clinic population in Tables 20-24.

With regard to these characteristics the groups were reasonably well matched for demographic and initial clinical and biochemical variables. Using analysis of variance, GSA was higher in those randomised to urine testing ($p=0.04$), although fructosamine levels were lower ($p<0.01$), whilst the group randomised to blood glucose testing were younger than the urine testing and control groups ($p<0.05$), and the latter had a higher body mass index ($p=0.004$) and a longer duration of diabetes ($p<0.001$) than the study groups. The control group also had higher levels of serum urea ($p = 0.04$) and creatinine ($p<0.01$), lower levels of creatinine clearance ($p<0.01$) and fasting blood glucose ($p = 0.04$), and were more frequently negative for C-peptide ($p<0.01$), in comparison to the study groups, whilst the LDL cholesterol / apo B-ratio was higher and the HDL/LDL and HDL/total cholesterol ratio lower in those who were randomised to urine testing ($p<0.05$). Finally, the levels of blood pressure and the prevalence of ischaemic heart disease and proliferative retinopathy were greater in the control population.

Table 20

DEMOGRAPHIC CHARACTERISTICS OF STUDY AND CONTROL GROUPS AT ENTRY TO STUDY.

	INITIAL RECRUIT	RANDOMISATION AT 6-8 WEEKS BLOOD GLUCOSE TESTING WITH METER	URINE STICKS TESTING FOR GLUCOSE	CLINIC CONTROL GROUP
TOTAL NO OF PATIENTS	153	68	79	52
MALE SEX (NO. (%))	99 (64.7)	41 (60.2)	54 (68.4)	29 (55.8)
AGE (YEARS)	40 (1)	38 (2) *	43 (2)	44 (2) *
BODY MASS INDEX (Kg/m^2)	23.6 (0.3)	23.0 (0.4)	24.1 (0.4)	26.1 (0.5)**
AGE AT DIAGNOSIS OF DIABETES (YEARS)	27 (1)	26 (2)	29 (2)	27 (2)
DURATION OF DIABETES (YEARS)	13 (1)	12 (1)	14 (1)	17 (1) +
PREVIOUS ORAL HYPOGLYCAEMIC TREATMENT (NO.(%))	50 (32.6)	22 (32.3)	28 (35.4)	16 (30.8)
DAILY INSULIN DOSE (UNITS)	51 (1)	52 (2)	50 (2)	49 (2)
DAILY INSULIN INJECTIONS (No.)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)	1.5 (0.1)
PATIENTS USING SOLUBLE INSULIN (No. (%))	70 (46)	32 (47)	35 (44)	20 (38)
TYPE OF INSULIN No (%)				
BEEF	80 (52%)	34 (50%)	42 (53%)	25 (48%)
HUMAN	52 (34%)	24 (35%)	27 (34%)	20 (39%)
PORCINE	21 (14%)	10 (15%)	10 (13%)	7 (13%)

* $P<0.05$ **$P = 0.004$ + $P<0.001$ Blood testing different from urine testing, study group different from control group.

Table 21

CHARACTERISTICS OF STUDY AND CONTROL GROUPS AT ENTRY TO STUDY.

	INTITAL RECRUIT	RANDOMISATION AT 6-8 WEEKS BLOOD TESTING	URINE TESTING	CONTROL GROUP
TOTAL NO OF PATIENTS	153	68	79	52
SMOKERS (%)	47%	51%	46%	45%
ALCOHOL (U/WEEK)	3.0 (0-60)	3.6 (0-40)	3.8 (0-60)	3.5 (0-50)
REGULAR EXERCISE (%)	45	46	44	40
EMPLOYMENT STATUS No (%)				
EMPLOYED	98 (64%)	39 (57%)	58 (73%)	35 (67%)
HOUSEWIFE	27 (18%)	*16 (24%)	8 (10%)	4 (7%)
UNEMPLOYED SEEKING WORK	18 (12%)	9 (13%)	7 (9%)	6 (12%)
RETIRED	9 (6%)	3 (4%)	6 (8%)	5 (10%)
SICK NOT SEEKING WORK	1 (1%)	1 (1%)	0 (0%)	2 (4%)
PATIENTS' SOCIAL CLASS (No (%))				
I	9 (6%)	3 (4%)	6 (8%)	3 (6%)
II	15 (10%)	6 (9%)	7 (9%)	3 (6%)
III	29 (19%)	12 (18%)	17 (22%)	15 (29%)
IV	45 (29%)	21 (31%)	22 (28%)	23 (44%)
V a	29 (19%)	16 (24%)	13 (16%)	4 (8%)
b	26 (17%)	10 (15%)	14 (17%)	4 (8%)
MARITAL STATUS (No (%))				
MARRIED	102 (67%)	46 (68%)	53 (67%)	32 (62%)
SINGLE	32 (21%)	14 (21%)	16 (20%)	8 (15%)
DIVORCED	7 (5%)	2 (2.5%)	4 (5%)	6 (12%)
WIDOWED	10 (7%)	4 (6%)	6 (8%)	5 (10%)
COHABITING	2 (1%)	2 (2.5%)	0 (0%)	1 (2%)

*$p<0.05$ Blood group different from the urine testing group.

Table 22 PREVALENCE OF COMPLICATIONS IN STUDY AND CONTROL GROUPS AT ENTRY TO THE STUDY

	INITIAL RECRUIT	RANDOMISATION AT 6-8 WEEKS BLOOD TESTING	URINE TESTING	CONTROL GROUP
TOTAL No. OF PATIENTS	153	68	79	52
ISCHAEMIC HEART DISEASE NUMBER (%)	16 (10%)	6 (9%)	10 (13%)	***12 (23%)
PERIPHERAL VASCULAR DISEASE NUMBER (%)	15 (10%)	7 (10%)	8 (10%)	7 (13%)
BACKGROUND RETINOPATHY NUMBER (%)	63 (41%)	30 (44%)	33 (42%)	***10 (19%)
PROLIFERATIVE RETINOPATHY NUMBER (%)	33 (22%)	15 (22%)	18 (23%)	***20 (38%)
PREVIOUS LASER PHOTOCOAGULATION NUMBER (%)	13 (8%)	7 (10%)	6 (8%)	5 (10%)
CLINICAL NEPHROPATHY NUMBER (%)	45 (29%)	20 (29%)	25 (32%)	22 (42%)
PERIPHERAL NEUROPATHY SCORE *(1-16)	13.4 (0.3)	13.9 (0.4)	12.8 (0.4)	12.9 (0.3)
AUTONOMIC NEUROPATHY SCORE (1-10)	2.1 (0.2)	1.9 (0.3)	2.3 (0.3)	2.0 (0.3)
IMPOTENCE (% MEN)	41	38	44	40
SYSTOLIC PRESSURE (mmHg)	133 (2)	131 (2)	134 (3)	147 (4)*
DIASTOLIC PRESSURE (mmHg)	76 (1)	74 (1)	77 (2)	83 (2)+
PREVALENCE OF HYPERTENSION NUMBER (%)	24 (16%)	9 (13%)	14 (18%)	14 (27%)

** P<= 0.005 *** P=0.001 Control group different from study groups. Figures are mean (SEM) or as stated.

Table 23

BIOCHEMICAL FEATURES OF STUDY AND CONTROL GROUPS AT ENTRY TO STUDY.

	INITIAL RECRUIT	RANDOMISATION AT 6-8 WEEKS		CONTROL GROUP
		BLOOD TESTING	URINE TESTING	
RENAL				
RENAL THRESHOLD FOR GLUCOSE (NUMBER (%))				
HIGH (> 12 mmol/L)	12 (8%)	7 (10%)	4 (5%)	5 (10%)
MEDIUM (8-11 mmol/L)	70 (46%)	34 (50%)	34 (43%)	25 (48%)
LOW (< 8 mmol/L)	71 (46%)	27 (40%)	41 (52%)	22 (42%)
SERUM UREA (mmol/L)	5.3 (0.2)	5.3 (0.2)	5.3 (0.1)	5.9 (0.3)*
SERUM CREATININE (µmol/L)	81 (2)	79 (2)	82 (2)	94 (4)**
CREATININE CLEARANCE (ml/min/1.73m^2)	132 (5)	133 (5)	132 (4)	93 (4)**
URINARY PROTEIN EXCRETION (g/24 hrs)	0.22 (0.05-5.30)	0.22 (0.05-6.00)	0.22 (0.05-5.30)	0.26 (0.05-4.20)
GLYCAEMIA				
FASTING BLOOD GLUCOSE (mmol/L)	11.0 (0.7)	10.4 (0.7)	11.8 (0.7)	*9.5 (0.6)
MEAN BLOOD GLUCOSE (mmol/L)	12.5 (0.3)	12.1 (0.5)	13.0 (0.4)	11.7 (0.4)
M VALUE (units)	119 (9)	113 (9)	127 (9)	120 (10)
HbA_1 (%)	9.2 (0.2)	9.2 (0.2)	9.3 (0.2)	9.5 (0.2)
GSA (%)	9.8 (0.4)	9.0 (0.5)	10.5 (10.5)*	-
FRUCTOSAMINE mmol/L (No)	4.13 (0.08)	4.30 (0.09)	4.00 (0.08)**	-
C- PEPTIDE STATUS				
C PEPTIDE NEGATIVE (No (%))	67 (44%)	37 (54%)	24 (30%)	43 (83%)**
C-PEPTIDE VALUE (pmol/ml)	0.005 (0.00-2.50)	0.001 (0.00-1.25)	0.03 (0.00-2.50)	0.001 (0.00-0.60)

* p = 0.04 ** p<0.01 Control v Study Groups, Blood v Urine testing group. Figures are mean (SEM), median (range).

Table 24 LIPIDS AND LIPOPROTEINS IN STUDY AND CONTROL GROUPS AT TRIAL ENTRY.

	INITIAL RECRUIT	RANDOMISATION BLOOD TESTING	AT 6-8 WEEKS URINE TESTING	CONTROL GROUP
TOTAL SERUM TRIGLYCERIDES (mmol/L)	1.29 (0.36-23.29)	1.10 (0.36-23.29)	1.29 (0.39-8.15)	1.35 (0.39-5.40)
TOTAL SERUM CHOLESTEROL (mmol/L)	5.66 (0.18)	5.58 (0.18)	5.70 (0.17)	5.93 (0.20)
LDL CHOLESTEROL (mmol/L)	3.78 (0.12)	3.59 (0.17)	3.92 (0.16)	3.48 (0.19)
HDL_{uc} CHOLESTEROL (mmol/L)	1.45 (0.03)	1.50 (0.04)	1.42 (0.04)	1.44 (0.05)
HDL_{2uc} CHOLESTEROL (mmol/L)	0.73 (0.031)	0.77 (0.04)	0.69 (0.04)	0.68 (0.04)
HDL_{3uc} CHOLESTEROL (mmol/L)	0.72 (0.02)	0.73 (0.03)	0.72 (0.03)	0.76 (0.03)
APOLIPOPROTEIN B (mg/dL)	101 (2)	104 (3)	99 (3)	109 (4)
LDL CHOLESTEROL / APO B	1.50 (0.05)	1.41 (0.07)	1.57* (0.06)	1.33* (0.04)
HDL / LDL	0.44 (0.02)	0.49 (0.03)	0.41* (0.02)	0.47 (0.03)
HDL / TOTAL CHOLESTEROL	0.27 (0.81)	0.29 (0.01)	0.26* (0.01)	0.25* (0.01)

* $p<0.05$ Study v Control Group, Blood v Urine testing group.
Figures are mean (SEM), median (range).

1:3. ASSESSMENT OF PATIENTS' SELF MANAGEMENT SKILLS, KNOWLEDGE ABOUT DIABETES AND ATTITUDES REGARDING DIABETES

The questionnaire designed to evaluate diabetic practice and knowledge and attitudes amongst those 153 insulin-treated diabetics originally recruited is contained in the initial trial entry document. (Appendix 1). The clinical characteristics of the group can be seen in figures (A-E).

GENERAL KNOWLEDGE: 1) (88%) felt that regular clinic attendance was important. Of these, 95 (70%) felt that attendance allowed glycaemic control to be checked, 18 (13%) suggested that clinics provided the opportunity to screen for diabetic complications, and 9 (7%) that clinics served to allow management of active problems. Only 13 (10%) felt that diabetic clinics operated on all these levels.

2) An adequate definition of diabetes (with mention of key words pancreas, insulin and blood glucose) was forthcoming in only 99 (65%) of cases.

3) 41 (27%) of the subjects did not think normal blood glucose levels were important provided that they felt alright.

INSULIN INJECTION 1) 130 (85%) were on highly purified insulin initially, and as many as 55 (41%) administered insulin once daily. 39 (25%) still used glass syringes, but the majority (75%) had used disposable syringes for some time.

2) The most popular injection sites were the legs (84% of cases), and thereafter the abdomen (48%),

arms (39%) and buttocks (10%). Only 89 (58%) were in the practice of regularly rotating injection sites. 48 (31%) had experienced lumps or pitting at injection sites.

3) Although only 3 of the 153 volunteered any difficulty drawing up their insulin, 28 (18%) were found to have problems with mixing insulins or with their injection technique. The commonest problems encountered were failing to break the vacuum in the vials by injection of air, or swabbing the skin with alcohol. In addition many doses were drawn up with isophane added to the vial prior to soluble when mixing insulins.

URINANALYSIS 1) 22% of patients did NOT monitor their urine for glycosuria. Of the 119 who did, 71 (60%) performed double voiding to improve the accuracy of recording and only 49 (41%) of them tested for ketonuria at any time. 55 (46%) tested their urine before meals, 10 (8%) after meals and the majority (45%) at either time.

2) Clinitest tablets, which give a qualitative measure of glycosuria, were used by 50 (42%) patients. Of the quantitative measures of glycosuria, Diastix was used more frequently (39%) than Clinistix (12%).

3) The majority (61%) monitored their urine daily, but 21% of patients only assessed glycosuria weekly, 3% performed monthly tests and testing was even less frequent in the remaining 15% of cases.

4) Urinanalysis was said to be most commonly negative for glycosuria in 32% of cases. 0.1% glycosuria

was reported as the most common result in 9 (7%), 0.25% in 5 (4%) of cases, 0.5% in 8 (7%), 1.0% in 22 (18%) and 2.0% in 18 (15%). 19 (16%) of the patients said glycosuria was too variable to declare which degree of glycosuria was most common.

5) The technique for urinanalysis was examined in all 153 patients, and found to be inadequate in 27 (17%) cases. The commonest sources of error were failure to record the time or result accurately or a simple inability to read the result accurately. In addition the concept of the 'percentage' of glycosuria was often not understood by patients.

HYPOGLYCAEMIA 1) 8 (5%) of the patients claimed never to have experienced episodes of hypoglycaemia. Of the 145 who did, 15 (10%) experienced symptoms daily, 22 (14%) weekly, 12 (8%) monthly, and the majority (96 (63%)) less frequently.

2) 59 (41%) usually experienced nocturnal hypoglycaemia, 18 (12%) usually had symptoms during the day, and in 10 (7%) cases hypoglycaemia was most common in the evening. For the remaining 40% the timing of hypoglycaemic episodes was unpredictable.

3) On enquiry as to the number of symptoms of hypoglycaemia each patient knew, 6 (4%) of the total group of 153 could not recollect any symptoms of hypoglycaemia. 50 (33%) knew at least 5 symptoms of hypoglycaemia and the mean number of symptoms recalled was 3.5. The commonest reported symptoms of hypoglycaemia were sweating (64%), shivering (32%), faintness (32%), blurred vision (20%), hunger (15%) and perioral paraesthesiae (15%). The full list of symptoms is seen in Table 25.

4) Reactions were attributed to excessive exercise (42%), missed or delayed meals (27%) or excessive insulin (11%). 21% had unexplained reactions. 74% always experienced premonitory symptoms, whilst in 4% of cases hypoglycaemia was unheralded.

5) All but 2 patients knew to take carbohydrate when symptoms devloped. However as many as 20% (31) did not always carry a carbohydrate source with them, and 24 (13%) did not routinely carry diabetic identification with them.

HYPERGLYCAEMIA / KETOACIDOSIS 1) 107 (70%) of the 153 had experienced at least 1 previous episode of ketoacidosis, but only 52% of the total group recognised specific symptoms or signs of ketoacidosis. 26 of the 49 patients who tested for ketonuria reported detection of ketones at some stage.

2) All but four patients were able to volunteer symptoms of hyperglycaemia. The symptoms reported are in Table 26.

3) In the context of hyperglycaemia associated with illness, only 37% (57 cases) would have taken extra insulin, 23 (15%) would have contacted their General Practitioner, and 3 (2%) would have contacted the hospital for advice. More importantly, 42% of patients would have taken the wrong action or were uncertain what to do.

Table 25. REPORTED SYMPTOMS OF HYPOGLYCAEMIA AND THEIR PREVALENCE IN 147 INSULIN-TREATED DIABETICS

SYMPTOM	PREVALENCE (%)
SWEATING	64
SHIVERING	32
FAINTNESS	32
BLURRED VISION	20
HUNGER	15
PERIORAL PARAESTHESIAE	15
LETHARGY	10
CONFUSION	9
LIMB PARAESTHESIAE	7
'MOODINESS'	7
HEADACHE	7
SLURRED SPEECH	5
INABILITY TO CONCENTRATE	4
AMNESIA	4
'CLUMSINESS'	3
STAGGERING	1
'NERVOUSNESS'	1
COLD FEET	1
HEAVY LIMBS	1
ABDOMINAL PAIN	1
NAUSEA	0.7
AGGRESSIVE	0.7
PALPITATIONS	0.3

Table 26. REPORTED SYMPTOMS OF HYPERGLYCAEMIA AND THEIR PREVALENCE IN 149 INSULIN-TREATED DIABETICS

SYMPTOM	PREVALENCE (%)
POLYDYPSIA	43
POLYURIA	25
FATIGUE	19
WEIGHT LOSS	13
NAUSEA - VOMITING	6
'BAD TEMPER'	5
DRY MOUTH	3
SWEET TASTE IN MOUTH	3
HEADACHE	3
BLURRED VISION	2
PRURITUS	1
ANOREXIA	0.7
ABDOMINAL PAIN	0.7
COLD DRY SKIN	0.7
LABOURED RESPIRATION	0.7
MYALGIA	0.7
INFECTIONS	0.7
DEPRESSION	0.7
'BLOATED FEELING'	0.7
UNWELL	0.7
SWEATING	0.7

EDUCATIONAL ASSESSMENT A series of questions on various aspects of self-management was asked and each patient reponse was graded from 1 (excellent) to 5 (terrible).

1. INSULIN INJECTION / DOSAGE - Subjects were asked to adjust their current insulin regime on the basis of various hyperglycaemic and hypoglycaemic situations and reported on the simple kinetics of soluble and isophane insulin (time of onset and peak action and duration of action). They were asked whether they were in the practice of self-adjustment of their insulin regime. The mean score for the 144 patients interviewed was 3.0; 17% of cases were graded as poor or terrible.

2. HYPOGLYCAEMIA - I ascertained knowledge regarding the effects of altering insulin, diet or energy expenditure in inducing hypoglycaemia, and hypoglycaemic symptoms and how to deal with them. Regular carriage of sugar and diabetic identification was scored favourably. The mean score for 144 patients was 3.1, and 31% of cases were graded as poor or terrible.

3. GLUCAGON - We asked trial patients what glucagon was, when and how to use it, how it worked, whether it had been previously used, or whether a family member or friend had been trained to use it. The mean score was 4.7, which highlighted the fact that 86% of the study group were graded as terrible through no fault of their own as they had never been previously exposed to glucagon..

4. DIET - Patients were asked about the fibre and fat content of

their diets and the relative importance of these components. We asked them to identify from lists, those foods with predominant carbohydrate, fat or protein content. The mean score was 3.3, and poor dietary practice and knowledge (score 4 or 5) was observed in 39% of cases.

5. EXERCISE - Exercise was graded as strenuous, regular or sporadic. Patients were asked what alterations in their insulin dose and diet preceded, accompanied or followed exercise, and what effect exercise would have on blood glucose levels. We inquired about appreciation of the phenomenon of delayed hypoglycaemic responses to exercise and the potential importance of exercise. Regular and/or strenuous exercise was assessed. The mean score was 3.7, and 57% of cases led a sedentary existence without insight into the role of exercise in diabetes care.

6. ILLNESS - We enquired about the effect of illness on blood glucose levels; the mechanism of ketone body production, symptoms of impending ketoacidosis; dietary management; the use of extra insulin and the role of medical assistance in dealing with certain types of illness. No patient scored excellent in this area, and the mean score was 4.1, with 70% of subjects scoring poor or terrible.

ATTITUDES TO DIABETES 1. 94% of patients stated that they had accepted diabetes as part of their daily life, although 22% admitted to feeling depressed about having diabetes. (V.I.). 3% admitted to feeling hostile and 9% felt angry about being diabetic, although 5% felt fearful of their diabetes.

2. Patients were asked if they had any specific concern about diabetes complications. Gangrene/ foot amputations (26%) and blindness (24%) were the commonest concerns. (Table 27). Only 4% of patients expressed concern about renal failure, 3% about macrovascular disease, and no one volunteered awareness or anxiety about neuropathy, hypertension or cerebrovascular disease.

3. Foot care was felt to be important in 88% of cases, but 35% of patients did not examine their feet regularly. Foot problems were commonly recognised as being more common due to circulatory disease (20%) or infection (16%), less commonly to neuropathy (2%), or more usually a combination of these factors (48%).

4. A family history of diabetes was present in 45% of 153 cases, and roughly 21% of the 153 patients had a 1st degree relative with diabetes mellitus. 60% of the total group knew at least 1 other person with diabetes.

Comment

A disappointing but not unexpected lack of knowledge was apparent from the educational assessment. Patients were deficient in virtually all important basic aspects of diabetes self care: insulin injection, urinanalysis and awareness regarding management of hypoglycaemia and hyperglycaemia. Of most concern was lack of knowledge regarding self-care during incidental illness and a lack of exposure to glucagon in the vast majority of cases. In addition, diet patterns were found to be suboptimal. The dominant concern amongst patients regarding

amputation and blindness was expected. However there appeared to be a lack of awareness about renal failure and neuropathy and perhaps more importantly, cardiovascular disease.

Following these assessments, patients were instructed in modification of insulin and diet during illness, and glucagon was given to all patients where a responsible friend or relative was available who could be instructed on home blood glucose monitoring and subcutaneous glucagon administration. A marked improvement in virtually all aspects of diabetes knowledge and self-management was apparent at the end of the run-in period, which was maintained after 1 year (Table 28).

Table 27 CONCERN ABOUT DIABETIC COMPLICATIONS IN 147 DIABETICS AT INITIAL TRIAL ENTRY.

COMPLICATION	REPORTED CONCERN (% PREVALENCE)
GANGRENE/AMPUTATION	26
BLINDNESS	24
KIDNEY FAILURE	4
HYPOGLYCAEMIC COMA	2
PERIPHERAL VASCULAR DISEASE	2
DIABETIC KETOACIDOSIS	1
SEVERE INFECTIONS	1
SUDDEN DEATH/REDUCED LIFE EXPECTANCY	1
IMPOTENCE	0.7
HEART DISEASE	0.7
PREGNANCY IN DIABETES	0.7
CHANGE IN APPEARANCE	0.7
CONTRACEPTION DIFFICULTY	0.7
LIFE INSURANCE DIFFICULTY	0.7
HYPERTENSION	0
CORONARY HEART DISEASE	0
NEUROPATHY	0

Table 28

EDUCATIONAL ASPECTS IN TOTAL STUDY GROUP AFTER INITIAL INTENSIVE MANAGEMENT PERIOD AND AFTER 1 YEAR

	INITIAL	POINT OF RANDOMISATION	1 YEAR
No. OF PATIENTS	153	147	124
PATIENT KNOWLEDGE			
GENERAL	3.5 (0.1)	2.2 (0.1)****	2.6 (0.1)****
INSULIN INJECTION	2.9 (0.1)	2.2 (0.1)****	2.2 (0.1)****
HYPOGLYCAEMIA	3.2 (0.1)	3.3 (0.1)	2.0 (0.1)****
GLUCAGON	4.7 (0.1)	2.7 (0.1)****	3.0 (0.1)****
DIET	3.3 (0.1)	2.6 (0.1)****	2.6 (0.1)***
EXERCISE	3.7 (0.2)	3.1 (0.1)****	2.2 (0.1)****
ILLNESS	4.1 (0.1)	2.1 (0.1)****	3.1 (0.1)****
INSULIN INJECTION TECHNIQUE	2.9 (0.1)	2.1 (0.1)****	2.2 (0.1)****
BLOOD GLUCOSE MONITORING TECHNIQUE	3.0 (0.1)	2.0 (0.1)****	2.3 (0.1)****
URINE GLUCOSE MONITORING TECHNIQUE	2.9 (0.1)	2.6 (0.1)***	2.4 (0.1)***

*** p = 0.001 **** p = 0.0001 Figures are mean (SEM).

1:4 EFFECTS OF INITIAL INTENSIFICATION OF MANAGEMENT ON METABOLIC CONTROL

Significant reductions in all aspects of glycaemic control were apparent after 6 weeks at the point of randomisation (Table 29). In addition after only 2 weeks, there were obvious reductions not only in direct measures of glycaemia, but also in levels of GSA and fructosamine (Table 29). A more detailed examination of the relationships between direct measures of glycaemia and the different glycated blood proteins is discussed in Chapter 5.

Lipid and lipoprotein values also showed major differences after 6 weeks. Significant reduction were observed in total serum levels of cholesterol and triglycerides, as well as levels of LDL cholesterol, HDL_3 cholesterol and the mass ratio of cholesterol to apolipoprotein B within LDL (Table 30). Levels of apolipoprotein B and the total HDL and HDL_2 cholesterol did not alter appreciably over this period. A more detailed breakdown of these changes is discussed in Chapter 4.

Measures of glycaemic control and lipid metabolism improved markedly in those who were hyperlipidaemic at entry to the study (Table 31).

Table 29
CHANGES IN GLYCAEMIC CONTROL DURING INTENSIVE MANAGEMENT PERIOD

	RECRUITMENT (BASAL)	WEEK 2	WEEK 4	RANDOMISATION (WEEK 6)
No OF PATIENTS	153	147	147	147
HbA_1 (%)	9.3 (0.2)	-	-	*** 8.2 (0.1)
GSA (%)	9.8 (0.4)	*** 8.5 (0.3)	*** 7.5 (0.3)	*** 7.3 (0.3)
FRUCTOSAMINE (mmol/L)	4.13 (0.08)	*** 3.84 (0.07)	*** 3.80 (0.07)	*** 3.58 (0.07)
SERUM ALBUMIN (g/L)	44.3 (0.3)	43.7 (0.3)	43.8 (0.3)	43.7 (0.3)
CORRECTED FRUCTOSAMINE	3.75 (0.07)	*** 3.54 (0.07)	*** 3.49 (0.08)	*** 3.28 (0.07)
FASTING BLOOD GLUCOSE (mmol/L)	11.0 (0.05)	*** 7.4 (0.03)	*** 7.2 (0.03)	*** 7.4 (0.02)
MEAN BLOOD GLUCOSE (mmol/L)	12.5 (0.3)	*** 9.6 (0.2)	*** 9.1 (0.2)	*** 8.7 (0.2)
M Value (UNITS)	119 (6)	59 ***(5)	47 ***(3)	42 ***(3)
24 HR URINE GLUCOSE EXCRETION (mmol/24hrs)	203 (18)	-	-	-
FASTING URINE GLUCOSE (SCORE)	0.80 (0.14)	***0.67 (0.14)	***0.50 (0.10)	***0.40 (0.08)
MEAN URINE GLUCOSE SCORE	0.97 (0.13)	**0.91 (0.12)	**0.68 (0.09)	***0.54 (0.07)

Figures are mean (SEM), median (range) ** p<0.01 *** p<0.001

Table 30

CHANGES IN LIPIDS AND LIPOPROTEINS DURING INTENSIVE MANAGEMENT PERIOD

	AT RECRUITMENT o		AT RANDOMISATION +
TRIGLYCERIDES mmol/l	1.29(0.36-23.29) 1.76 (0.17)	****	1.14 (0.24-19.36) 1.52 (0.17)
CHOLESTEROL mmol/l	5.64 (0.12)	****	5.26 (0.12)
LDL CHOLESTEROL mmol/l	3.78 (0.12)	***	3.46 (0.12)
APOLIPOPROTEIN B mg/dl	101 (2)		101 (2)
HDL_{uc} CHOLESTEROL mmol/l	1.46 (0.03)		1.40 (0.03)
HDL_{2uc} CHOLESTEROL mmol/l	0.73 (0.03)		0.76 (0.03)
HDL_{3uc} CHOLESTEROL mmol/l	0.73 (0.02)	***	0.64 (0.02)
$\frac{\text{HDL CHOLESTEROL}}{\text{LDL}}$	0.44 (0.02)		0.46 (0.02)
$\frac{\text{HDL CHOLESTEROL}}{\text{TOTAL}}$	0.27 (0.01)		0.29 (0.02)
$\frac{\text{LDL CHOLESTEROL}}{\text{APO B}}$	1.50 (0.05)	**	1.37 (0.04)

o number = 147
+ number = 137

Figures are mean (SEM) or median (range)

** p<0.01 *** p<0.005 **** p<= 0.0001

Table 31.

CHANGES IN GLYCAEMIC CONTROL AND LIPID METABOLISM IN 57 HYPERLIPIDAEMIC SUBJECTS DURING THE INTENSIVE MANAGEMENT PERIOD.

	Initial	After Intensive Management
Number of subjects	57	26
HbA_1 (%)	9.6 (0.6)	8.3 (0.5) ***
Total Cholesterol (mmol/l)	7.00 (0.22)	5.89 (0.34) ***
Total Triglycerides (mmol/l)	3.00 (0.36 - 23.29)	1.65 (0.34 - 19.39) ***
LDL Cholesterol (mmol/l)	5.00 (0.24)	4.02 (0.28) ***
HDL Cholesterol (mmol/l)	1.34 (0.07)	1.27 (0.08)
HDL_2 Cholesterol (mmol/l)	0.66 (0.05)	0.69 (0.07)
HDL_3 Cholesterol (mmol/l)	0.68 (0.06)	0.58 (0.06)**
Apolipoprotein B (mg%)	113 (7)	108 (6)

Figures are mean (SEM) or median (range).

*** $p<0.001$ ** $p<0.05$

1.5 COMPARISON OF BLOOD AND URINE GLUCOSE MONITORING GROUPS IN THE FIRST YEAR OF THE STUDY

Following the period of intensive management and optimisation of control, 68 individuals were randomised to blood glucose testing, of whom 61 (90%) completed the first year of the study, whilst 79 commenced urine glucose monitoring of whom 63 (80%) completed the first year of the study. The higher drop-out rate in the urine testing group ($p<0.05$), was mainly due to withdrawal at the point of randomisation when most refused to stop blood glucose monitoring. The fall off in patient numbers in blood and urine glucose testing groups is seen in Table 32.

Table 32 RATE OF DROP-OUT IN BLOOD AND URINE GLUCOSE MONITORING GROUPS DURING 1ST YEAR OF THE STUDY

	Point of Randomisation	Mth 3	Mth 6	Mth 9	1 yr
Blood Glucose Testing Group	68	65	62	61	61
Urine Glucose Testing Group	79 *	71	68	67	63

Figures refer to numbers of patients still in study (*$p<0.05$)

The clinical and biochemical characteristics at entry to the study of those ultimately randomised to either blood or urine testing are shown in Tables 20-24. The two groups were comparable in all respects apart from levels of GSA and the age of patients which were significantly higher at study entry in those randomised to urine testing ($p = 0.04$) although GSA levels closely approximated in the two groups at the point of

randomisation.

Metabolic Control

GLYCAEMIC CONTROL

Levels of glycosylated haemoglobin (HbA_1) were equivalent in both groups at entry to the study and at point of randomisation when a significant fall ($p<0.001$) from baseline level was apparent in both groups. Thereafter HbA_1 levels remained more stable in the urine glucose monitoring group whilst a non-significant trend towards further reduction in HbA_1 was observed in the blood glucose monitoring group, and the difference was significant ($p<0.02$) after 6 months (Figure 14).

Fasting and mean blood glucose levels and the M-values were assessed from monthly filter card blood glucose profiles. The degree of compliance was variable between the two groups. The number of completed returned patient profiles per month is shown in Table 33. The response rate varied between 69% and 85% in the blood testing group (mean response rate 78%) which was significantly higher than the urine glucose monitoring group, where the response rate varied between 63 and 86% (mean response rate 68%) ($p<0.05$). Notwithstanding the poorer response in the urine testing group, fasting filter paper blood glucose levels were significantly higher in the urine glucose monitoring group at months 5, 6 and 8 ($p< 0.05$), (Figure 15) whilst mean filter paper blood glucose levels were higher in the urine monitoring group at months 3,4,5,6,8,11 and 12 ($p<0.04 - 0.001$) (Figure 16).

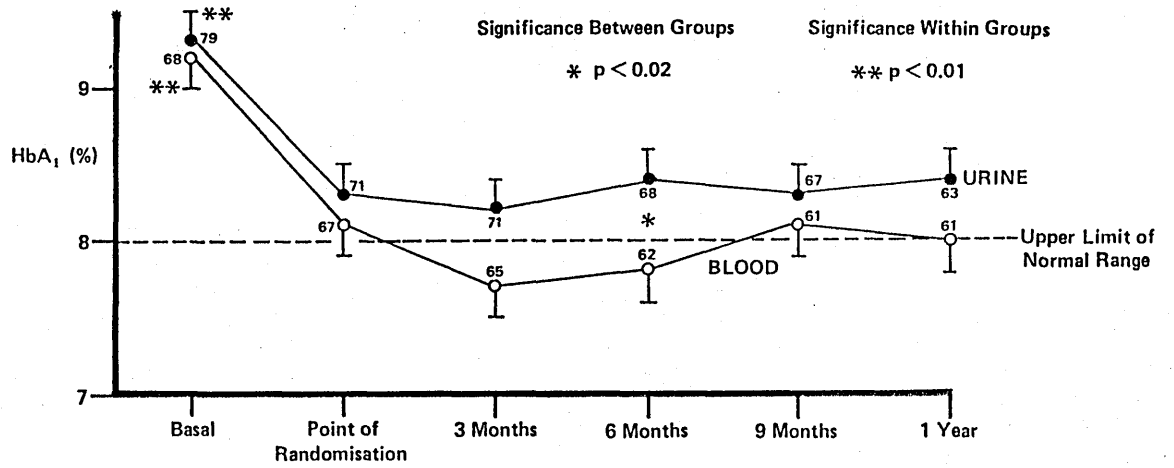


FIG. 14 Comparison of changes in HbA_1 in urine and blood glucose testing groups during the 1st year of the study.

Figures represent Mean ± SEM

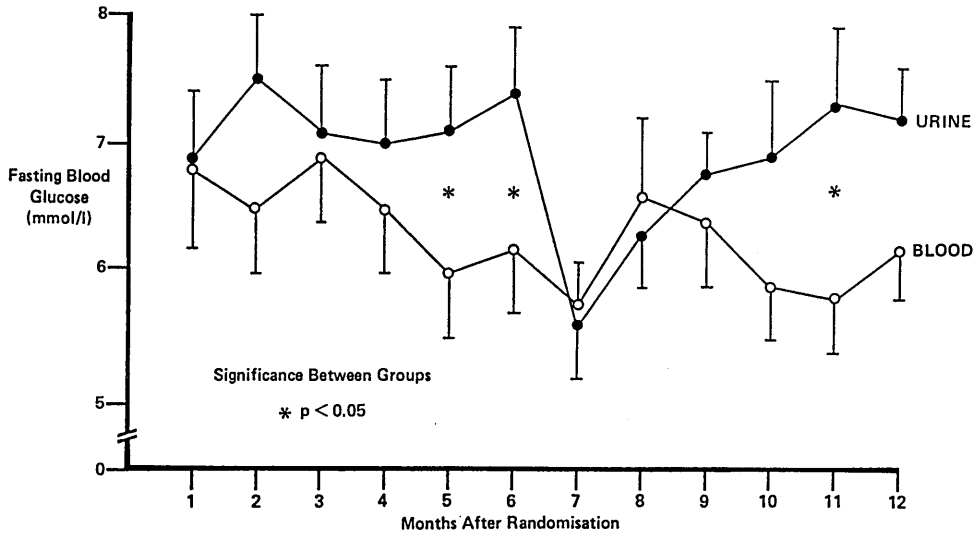


FIG. 15 Comparison of changes in filter paper fasting blood glucose levels in urine and blood glucose testing groups during the 1st year of the study.

Figures represent Mean ± SEM

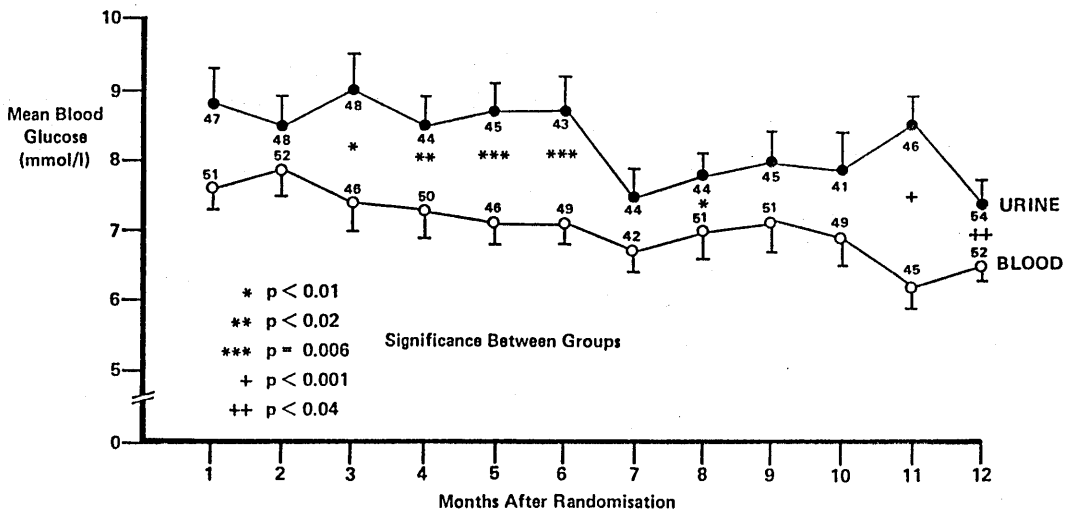


FIG. 16 Comparison of changes in filter paper mean blood glucose levels in urine and blood glucose testing groups during the 1st year of the study.

Figures represent Mean ± SEM

A similar pattern also emerged with regard to filter paper M- values, which remained higher in the urine glucose monitoring group at months 3,4,5,6,8,10,11 and 12 ($p<0.03$-0.01) (Figure 17).

TABLE 33. NUMBER OF COMPLETED PROFILES (% RESPONSE RATE OF PATIENTS) SUITABLE FOR ANALYSIS IN BLOOD AND URINE GLUCOSE MONITORING GROUPS.

MONTH	BLOOD GLUCOSE MONITORING	URINE GLUCOSE MONITORING
1	51 (78%)	47 (66%)
2	52 (80%)	48 (68%)
3	46 (71%)	48 (68%)
4	50 (81%)	44 (65%)
5	46 (74%)	45 (66%)
6	49 (79%)	43 (63%)
7	42 (69%)	44 (66%)
8	51 (84%)	44 (66%)
9	51 (84%)	45 (67%)
10	49 (80%)	41 (65%)
11	45 (74%)	46 (73%)
12	52 (85%)	54 (86%)

A significant difference in GSA levels was seen during the year in both blood and urine glucose monitoring groups. The lowest levels were seen at the point of randomisation when they were comparable in the two groups. Those randomised to urine testing had significantly higher levels at recruitment to the study and also after 3 months ($p<0.05$), and GSA levels tended to be higher throughout the study in the urine testing group (Figure 18). As with GSA levels, levels of fructosamine varied significantly during the study in both blood and urine glucose monitoring groups. In comparison to the blood testing group, the

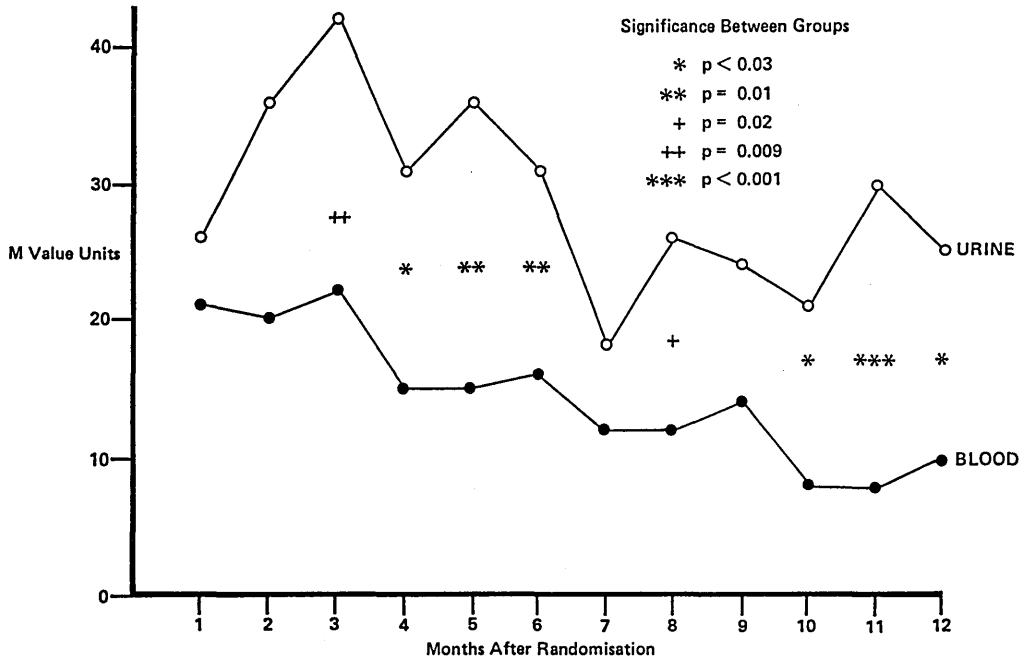


FIG. 17 Comparison of changes in filter paper M values in urine and blood glucose testing groups during the 1st year of the study.

Figures represent Median

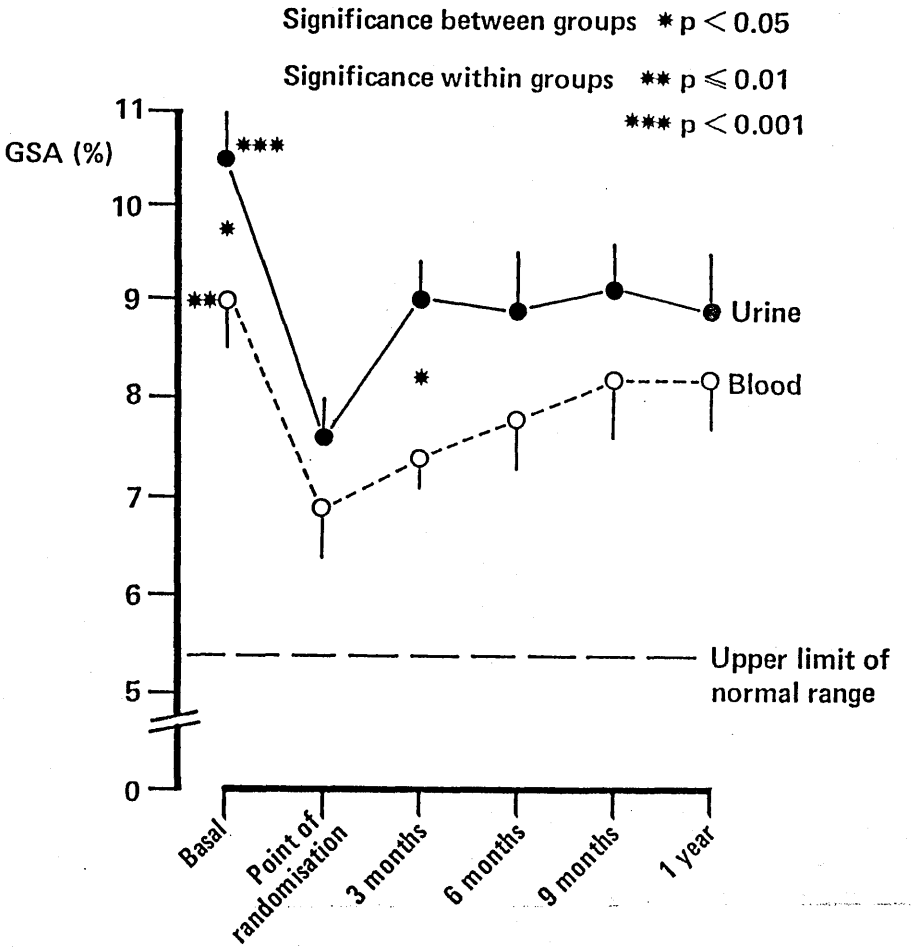


FIG. 18 Comparison of changes in GSA in urine and blood monitoring groups during the 1st year of the 1st year of the study.

Figures represent Mean ± SEM

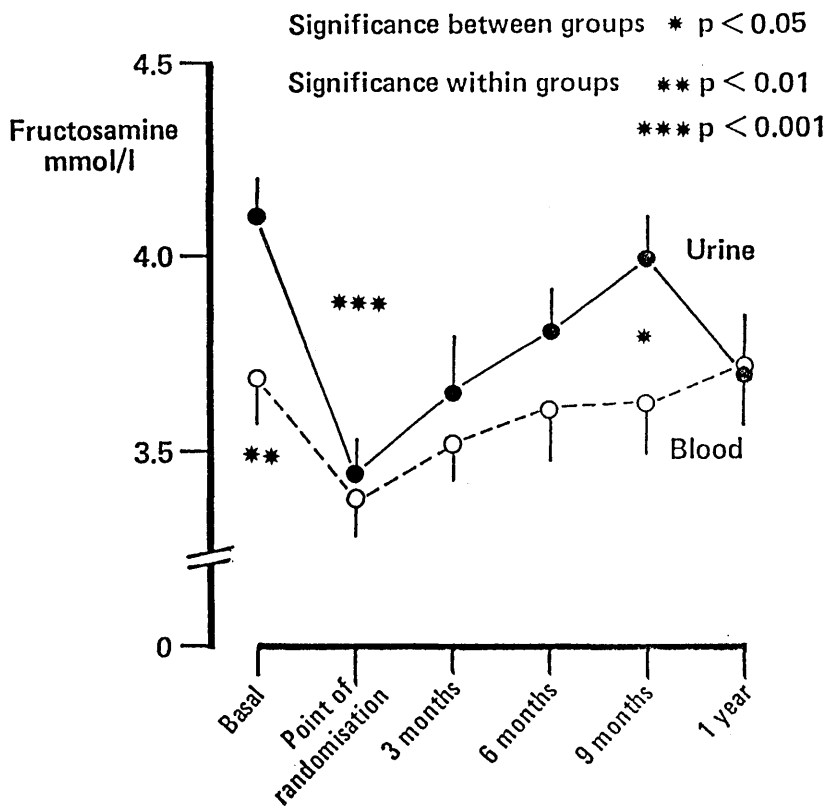


FIG. 19 Comparison of changes in fructosamine in urine and blood glucose monitoring groups during the 1st year of the study.

Figures represent Mean ± SEM

urine testing group had significantly higher fructosamine levels at the outset of the study ($p<0.01$) and also after 9 months ($p<0.05$), but levels were indistinguishable after 1 year (Figure 19).

The number of episodes of hospital admissions in the 1st year with diabetic ketoacidosis was similar in both groups (blood testing 4, urine testing 5). The frequency of symptomatic hypoglycaemia and number of patients who had experienced at least one episode was assessed every 3 months, and did not differ appreciably between the two groups. No assessment of the severity of hypoglycaemia was made (Table 34).

Likewise there was no apparent difference in patient satisfaction with the respective methods of monitoring and degree of control between the blood and urine testing groups. (Table 34).

LIPIDS AND LIPOPROTEINS (Table 35)

Apart from higher triglyceride levels initially in those randomised to urine testing ($p<0.05$), there were no differences throughout the first year of the study between the blood and urine glucose monitoring groups with regard to levels of triglycerides or total cholesterol, LDL and HDL cholesterol, the HDL_2 and HDL_3 cholesterol subfractions, or levels of apolipoprotein B. Likewise the ratios of LDL cholesterol/apo B, HDL/LDL cholesterol and HDL/total cholesterol remained similar in both groups during the 1st year of the year, although the LDL cholesterol/apo B ratio was higher initially in those randomised to urine testing (Table 35).

CARBOHYDRATE INTAKE / WEIGHT (Table 36)

Body mass index (BMI) and weight was higher at initiation to the study in those randomised to urine testing although thereafter they were comparable. However a graded increase in BMI and weight was apparent after 6 months which rose further after 9 months and 1 year, irrespective of the means of monitoring metabolic control, and despite no apparent change in the alleged carbohydrate intake.

Table 34 INCIDENCE OF HYPOGLYCAEMIC AND KETOACIDOTIC EPISODES AND SATISFACTION WITH DEGREE/METHOD OF CONTROL IN BLOOD AND URINE GLUCOSE MONITORING GROUPS

	BLOOD TESTING	URINE TESTING
EPISODES OF DIABETIC KETOACIDOSIS DURING THE 1ST YEAR	4	5
MONTHLY RATE OF SYMPTOMATIC HYPOGLYCAEMIA.		
1. RANDOMISATION - MONTH 3		
No. OF PATIENTS WITH AT LEAST ONE EPISODE (%)	40 (62%)	42 (59%)
FREQUENCY	1.1 (0-20)	1.0 (0-10)
2. MONTH 3 - MONTH 6		
No. OF PATIENTS WITH AT LEAST ONE EPISODE (%)	33 (53%)	41 (60%)
FREQUENCY	0.7 (0-28)	1.1 (0-30)
3. MONTH 6 - MONTH 9		
No. OF PATIENTS WITH AT LEAST ONE EPISODE (%)	35 (57%)	45 (67%)
FREQUENCY	1.1 (0-29)	1.3 (0-28)
4. MONTH 9 - MONTH 12		
No. OF PATIENTS WITH AT LEAST ONE EPISODE (%)	32 (52%)	37 (59%)
FREQUENCY	0.6 (0-10)	0.8 (0-5)
PATIENT SATISFACTION WITH METHOD/DEGREE OF CONTROL NUMBER (%)	49 (80%)	56 (84%)

TABLE 35

Serum lipid and lipoproteins in blood and urine glucose monitoring groups during the study

	TYPE OF GROUP	INITIAL	POINT OF RANDOMISATION	6 MONTHS	1 YEAR
TRIGLYCERIDES (mmol/l)	BLOOD	1.10 (0.36- 3.29)	1.14 (0.24-19.39)	1.04 (0.19-58.90)	1.09 (0.29-11.89)
	URINE	1.29 (0.39-8.15)	1.09 (0.34-9.38)	1.34 (0.24-6.44)	1.23 (0.44-8.90)
CHOLESTEROL (mmol/l)	BLOOD	5.58 (0.18)	5.29 (0.18)	5.63 (0.35)	5.48 (0.15)
	URINE	5.70 (0.17)	5.24 (0.16)	5.57 (0.19)	5.51 (0.17)
LDL CHOLESTEROL (mmol/l)	BLOOD	3.59 (0.17)	3.41 (0.15)	3.52 (0.17)	3.49 (0.14)
	URINE	3.92 (0.16)	3.50 (0.15)	3.76 (0.20)	3.32 (0.16)
APOLIPOPROTEIN B (mg/dL)	BLOOD	104 (3)	103 (3)	100 (3)	102 (3)
	URINE	99 (3)	99 (3)	105 (3)	104 (3)
LDL $\frac{\text{CHOLESTEROL}}{\text{Apo B}}$	BLOOD	1.41 (0.07)	1.32 (0.06)	1.35 (0.06)	1.37 (0.05)
	URINE	1.57 (0.06)*	1.48 (0.06)	1.46 (0.07)	1.27 (0.07)
HDL CHOLESTEROL (mmol/l)	BLOOD	1.50 (0.04)	1.40 (0.05)	1.40 (0.04)	1.46 (0.04)
	URINE	1.42 (0.04)	1.40 (0.05)	1.37 (0.04)	1.42 (0.04)
HDL_2 CHOLESTEROL (mmol/l)	BLOOD	0.73 (0.03)	0.77 (0.05)	0.74 (0.05)	0.72 (0.04)
	URINE	0.69 (0.04)	0.75 (0.04)	0.69 (0.04)	0.68 (0.04)
HDL_3 CHOLESTEROL (mmol/L)	BLOOD	0.77 (0.04)	0.63 (0.03)	0.66 (0.02)	0.75 (0.03)
	URINE	0.72 (0.03)	0.65 (0.03)	0.68 (0.03)	0.75 (0.03)
$\frac{\text{HDL CHOLESTEROL}}{\text{LDL}}$	BLOOD	0.49 (0.03)	0.46 (0.03)	0.47 (0.03)	0.46 (0.02)
	URINE	0.41 (0.02)	0.47 (0.03)	0.43 (0.03)	0.51 (0.04)
$\frac{\text{HDL CHOLESTEROL}}{\text{TOTAL}}$	BLOOD	0.29 (0.01)	0.25 (0.01)	0.28 (0.01)	0.28 (0.01)
	URINE	0.26 (0.01)	0.28 (0.03)	0.26 (0.01)	0.28 (0.1)

*$p < 0.05$

Table 36 CARBOHYDRATE INTAKE, WEIGHT AND BODY MASS INDEX (BMI) IN BLOOD AND URINE GLUCOSE TESTING GROUPS DURING THE FIRST YEAR OF THE STUDY

	BLOOD GLUCOSE TESTING			URINE GLUCOSE TESTING	
WEIGHT (kg)					
INITIAL	65.6 (1.5)		(*)	70.2 (1.2)	
RANDOMISATION	66.1 (1.5)			69.9 (1.3)	
MONTH 3	66.8 (1.4)			70.2 (1.3)	
MONTH 6	67.4 (1.3)	***	(*)	71.2 (1.3)	**
MONTH 9	68.0 (1.3)	***		71.9 (1.4)	***
YEAR 1	68.7 (1.4)	***		72.8 (1.4)	***
BMI					
INITIAL	23.0 (0.4)		(*)	24.1 (0.4)	
RANDOMISATION	23.2 (0.4)			24.1 (0.4)	
MONTH 6	23.6 (0.3)	***		24.4 (0.4)	**
YEAR 1	24.1 (0.4)	***		24.9 (0.4)	***
CARBOHYDRATE INTAKE (g/DAY)					
INITIAL	192 (9)			184 (6)	
POINT OF RANDOMISATION	185 (6)			185 (5)	
YEAR 1	184 (6)			185 (6)	

Significance within groups ** p = 0.004 *** p = 0.0001
Significance between groups (*) p = 0.04

Table 37 INDICES OF MICROVASCULAR AND MACROVASCULAR DISEASE IN BLOOD AND URINE GLUCOSE MONITORING GROUPS DURING THE STUDY

	Blood Testing Group		Urine Testing Group	
	Initial	1 year	Initial	1 year
NEPHROPATHY				
SERUM UREA (mmol/l)	5.3 (0.2)	5.1 (0.2)	5.3 (0.1)	5.2 (0.2)
SERUM CREATININE (µmol/l)	79 (2)	81 (2)	82 (2)	83 (2)
CREATININE CLEARANCE (ml/min)	133 (5)	125 (5)	132 (4)	112 (4)
AER (TOTAL) (µg/min)	6.9 (1.0-355.0)	5.4 (1.1-1000.0)	5.5 (0.3-625.0)	6.4 (1.5-1000.0)
AER (DAY) µg/min)	6.5 (0.9-398.0)	5.0 (0.5-884.4)	6.1 (0.1-690.0)	7.6 (0.9-1000.0)
AER (NIGHT) (µg/min)	5.3 (1.0-355.0)	3.7 (1.0-1000.0)	4.7 (0.2-999.8)	4.6 (0.7-1000.0)
% ALBUSTIX >0.3 g/L	9	3	11	8.
PERIPHERAL NEUROPATHY**			***	*
SCORE	13.9 (0.4)	13.6 (0.5)	12.8 (0.4)	12.2 (0.4)
AUTONOMIC NEUROPATHY SCORE	1.9 (0.3)	1.9 (0.3)	2.3 (0.3)	2.3 (0.3)
RETINOPATHY				
% NIL	34	43	35	32
% BACKGROUND	44	34	42	40
% PROLIFERATIVE	22	23	23	28
% ISCHAEMIC HEART DISEASE	9%	11%	13%	13%
% PERIPHERAL VASCULAR DISEASE	10%	9%	10%	13%

* p<0.05 within group ** p<0.02, *** p<0.002 between group

MICROVASCULAR AND MACROVASCULAR DISEASE (Table 37)

Various measures of renal and autonomic function were similar in both groups initially and after 1 year. Likewise the prevalence of ischaemic heart disease, peripheral vascular disease and retinopathy was no different in the blood or urine testing groups during the study. However the peripheral neuropathy score was initially higher in those who were randomised to blood testing ($p<0.02$) and fell in those doing urine testing ($p<0.05$) so that a highly significant difference was apparent between the 2 groups after 1 year ($p<0.002$).

INSULIN SPECIES, DOSAGE AND FORMULATION (Table 38)

The daily insulin dosage, soluble component or species did not differ between the 2 groups although a significant increase ($p<0.001$) in the number of patients in both groups using soluble insulin was apparent at the point of randomisation which continued during the 1st year of the study.

CONTACT WITH HEALTH PROFESSIONALS (Table 39)

More urine testing patients contacted their GP after 3-6 months ($p<0.05$), and they also lost more time off work after 3 and 6 months. However the blood testing group had made significantly more hospital contact after 6 months ($p<0.05$), and contacted me more often after the first 3 months ($p<0.05$).

EDUCATIONAL ASPECTS (Table 40)

Although educational scores were still improved in both groups after 1 year, knowledge about the role of exercise and management during illness appeared better in the blood testing groups after 1 year ($p<0.01$).

Table 38 INSULIN SPECIES, DOSAGE AND FORMULATION IN BLOOD (B) AND URINE (U) GLUCOSE MONITORING GROUPS DURING THE STUDY

		INITIAL	POINT OF RANDOMISATION	MONTH 3	MONTH 6	MONTH 9	MONTH 12
DAILY DOSE INSULIN (U)	B	52(2)	52(2)	52(3)	52(3)	52(3)	54(3)
	U	50(2)	49(2)	51(2)	51(2)	52(2)	52(2)
% ON MORNING SOLUBLE	B	47	51	49	60	64	67
	U	44	44	54	57	57	60
MORNING SOLUBLE DOSE	B	12.9 (1.9)	4.1 (0.7)	4.1 (0.7)	5.5 (0.9)	5.4 (0.9)	5.7 (0.9)
	U	10.4 (1.6)	3.4 (0.5)	3.9 (0.6)	4.8 (0.7)	4.7 (0.7)	4.7 (0.7)
% ON MORNING ISOPHANE	B	46	93***	94***	92***	90***	90***
	U	46	90***	92***	91***	91***	91***
MORNING ISOPHANE DOSE	B	13.5 (2.2)	30.8 (1.9)	31.2 (1.8)	30.3 (2.0)	29.6 (2.0)	30.1 (2.0)
	U	14.3 (2.0)	28.8 (1.7)	29.4 (1.7)	28.9 (1.7)	29.0 (1.8)	29.5 (1.9)
% ON EVENING SOLUBLE	B	26	19	28	37	43	51
	U	24	24	27	32	28	30
EVENING SOLUBLE DOSE	B	5.3 (1.3)	1.4 (0.5)	1.6 (0.5)	2.3 (0.6)	2.6 (0.6)	3.1 (0.6)
	U	4.9 (1.1)	1.3 (0.3)	1.4 (0.3)	2.3 (0.5)	2.1 (0.5)	2.0 (0.5)
% ON EVENING ISOPHANE	B	44	88**	86**	89**	85**	85**
	U	39	83**	83**	79**	81**	81**
EVENING ISOPHANE DOSE	B	6.4 (1.0)	12.6 (1.1)	12.3 (1.1)	12.6 (1.3)	11.6 (1.1)	11.7 (1.2)
	U	6.3 (1.0)	12.3 (1.1)	12.3 (1.1)	11.9 (1.2)	12.3 (1.2)	12.5 (1.3)
INSULIN SPECIES	B	56% B 38% H 6% P	49% B 33% H 18% P	51% B 34% H 17% P	52% B 32% H 15% P	52% B 32% H 16% P	51% B 34% H 15% P
	U	54% B 41% H 5% P	47% B 39% H 14% P	49% B 37% H 14% P	50% B 35% H 15% P	50% B 35% H 15% P	51% B 37% H 12% P

**p<0.01, ***p<0.001 different from initial. Mean (SEM).

Table 39 CONTACTS WITH HEALTH PROFESSIONALS AND WORK PATTERNS FOLLOWING RANDOMISATION IN BLOOD AND URINE GLUCOSE MONITORING

	GROUP							
	MONTH 3		MONTH 6		MONTH 9		1 YEAR	
	BLOOD	URINE	BLOOD	URINE	BLOOD	URINE	BLOOD	URINE
CONTACTS WITH DIABETIC NURSE								
TOTAL	14	12	2	7	3	0	1	2
PATIENTS WHO MADE CONTACT	6(9%)	4(6%)	2(3%)	5(7%)	3(3%)	0(0%)	1(2%)	2(3%)
CONTACTS WITH G.P.								
TOTAL	7	31*	14	30*	20	19	15	15
PATIENTS WHO MADE CONTACT	5 (8%)	16 (23%)	9 (15%)	18 (26%)	11 (18%)	11 (16%)	8 (13%)	9 (14%)
CONTACTS WITH CASUALTY								
TOTAL	4	6	8*	3	3	2	2	1
PATIENTS WHO MADE CONTACT	3(5%)	5(7%)	5(8%)	3(4%)	2(3%)	2(3%)	2(3%)	1(2%)
CONTACTS WITH TRIAL DOCTOR								
TOTAL	12*	6	15	8	17	16	1	1
PATIENTS WHO MADE CONTACT	10 (15%)	5 (7%)	8 (13%)	8 (12%)	10 (16%)	8 (12%)	1 (2%)	1 (2%)
INPATIENT ADMISSIONS								
TOTAL	1	1	1	1	2	3	1	1
No OF PATIENTS	1	1	1	1	2	3	1	1
DAYS OFF WORK DUE TO DIABETES								
No. WORKING	35	*55	35	46	34	44	34	44
TOTAL DAYS OFF	5	*15	0	*70	10	16	10	18
(AV.PER PATIENT)	0.14	*3.7	0	*1.5	0.3	0.4	0.3	0.4
No OF PATIENTS OFF WORK	1	3	0	4	1	1	2	2

* $p<0.05$

Figures are number $\pm$ (%).

Table 40 EDUCATIONAL ASPECTS IN BLOOD AND URINE GLUCOSE MONITORING GROUPS

	INITIAL		Randomisation to		1 YEAR	
	BLOOD	URINE	BLOOD	URINE	BLOOD	URINE
PATIENT KNOWLEDGE						
GENERAL	3.5(0.1)	3.5(0.1)	**** 2.2(0.1)	**** 2.2(0.1)	**** 2.5(0.1)	**** 2.7(0.1)
INSULIN INJECTION	2.9(0.1)	2.9(0.1)	**** 2.1(0.1)	**** 2.2(0.1)	**** 2.1(0.1)	**** 2.3(0.1)
HYPOGLYCAEMIA	3.1(0.1)	3.2(0.1)	3.3(0.1)	3.3(0.1)	**** 1.9(0.1)	**** 2.1(0.1)
GLUCAGON	4.7(0.1)	4.7(0.1)	**** 2.7(0.1)	**** 2.7(0.1)	**** 3.1(0.2)	**** 2.8(0.1)
DIET	3.4(0.1)	3.3(0.1)	**** 2.6(0.1)	**** 2.6(0.1)	**** 2.5(0.1)	**** 2.7(0.1)
EXERCISE	3.6(0.1)	3.7(0.1)	*** 3.1(0.1)	**** 3.0(0.1)	****(*) 2.0(0.1)	**** 2.4(0.1)
ILLNESS	4.1(0.1)	4.1(0.1)	**** 2.0(0.1)	2.2(0.1)	****(*) 2.8(0.1)	3.3(0.1)
INSULIN INJECTION TECHNIQUE	2.9(0.1)	2.8(0.1)	**** 2.1(0.1)	**** 2.0(0.1)	**** 2.2(0.1)	**** 2.3(0.1)
BLOOD GLUCOSE MONITORING TECHNIQUE	3.1(0.1)	2.9(0.1)	**** 2.0(0.1)	**** 2.1(0.1)	** 2.3(0.1)	--
URINE GLUCOSE MONITORING TECHNIQUE	3.0(0.1)	2.8(0.1)	**** 2.5(0.1)	*** 2.4(0.1)	--	*** 2.4(0.1)

(*) p<0.01 between groups

**p <0.01 *** p = 0.001 **** p = 0.0001 within groups

Figures are mean (SEM).

1:6 QUALITY CONTROL ASSESSMENT OF THE REFLOLUX METER AND PATIENT GENERATED HOME BLOOD GLUCOSE MONITORING RESULTS

Evaluation of the Reflolux blood glucose meter

Fasting blood values were measured by the biochemistry laboratory (Yellow Springs Analyser) and compared with the results that I obtained myself from the same samples using the Reflolux meter. Both measures use glucose oxidase to produce an enzymatic colorimetric reaction. This was repeated on 3 different occassions duing the study (at 6 weeks, 6 months and 1 year). The correlation between the 2 measures was highly significant over the range of blood glucose values for 63-106 measures (r ranging from 0.95-0.98, $p<0.0001$) (1 year data shown in figure 20(a)). However if only paired measures were compared when laboratory glucose values were reported as less than 3 mmol/l, no such relationship emerged ($r = 0.09$, p n/s) (figure 20(b). Furthermore there was a general tendency for Reflolux blood glucose values to be greater than that measured in the biochemistry laboratory (figure 20). The implication from these observations was that significant biochemical hypoglycaemia may not have been detected by patients with hypoglycaemic unawareness who were carrying out blood testing using the Reflolux machine. This impression was confirmed by comparing the laboratory based filter card glucose measurements with Reflolux readings subsequently carried out by patients during the study (v.i.).

Evaluation of patient generated blood glucose results

68 patients were randomised to self blood glucose monitoring

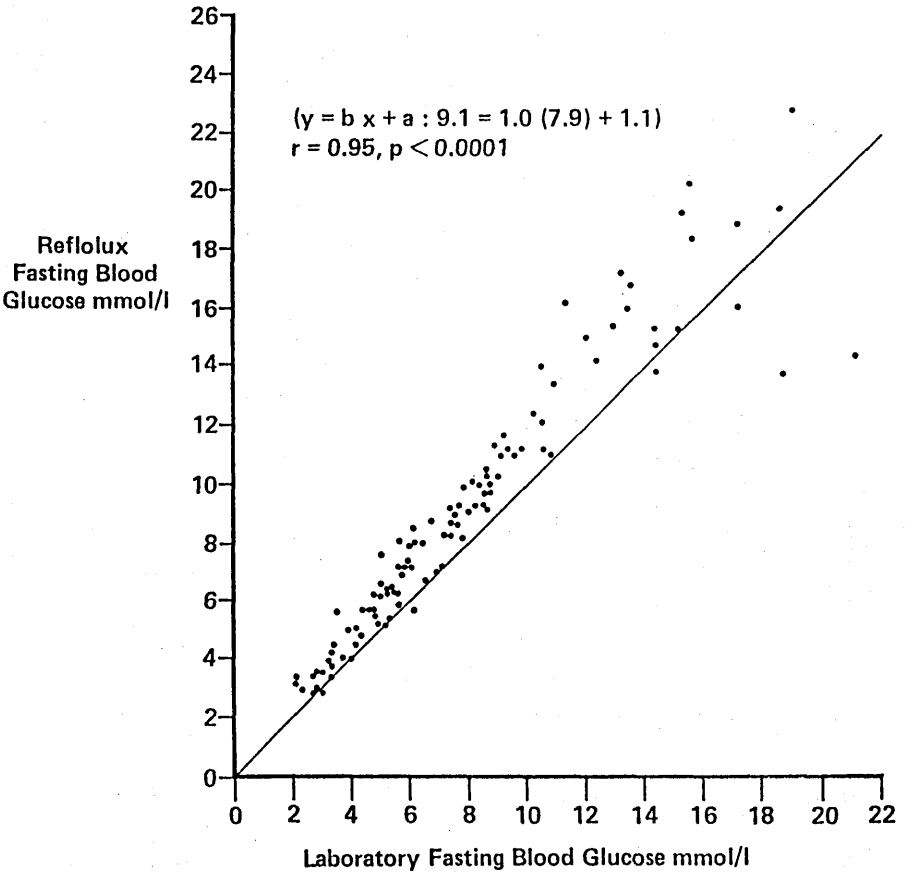


FIG. 20a Correlation between Reflolux and Yellow Springs fasting blood glucose levels; all levels.

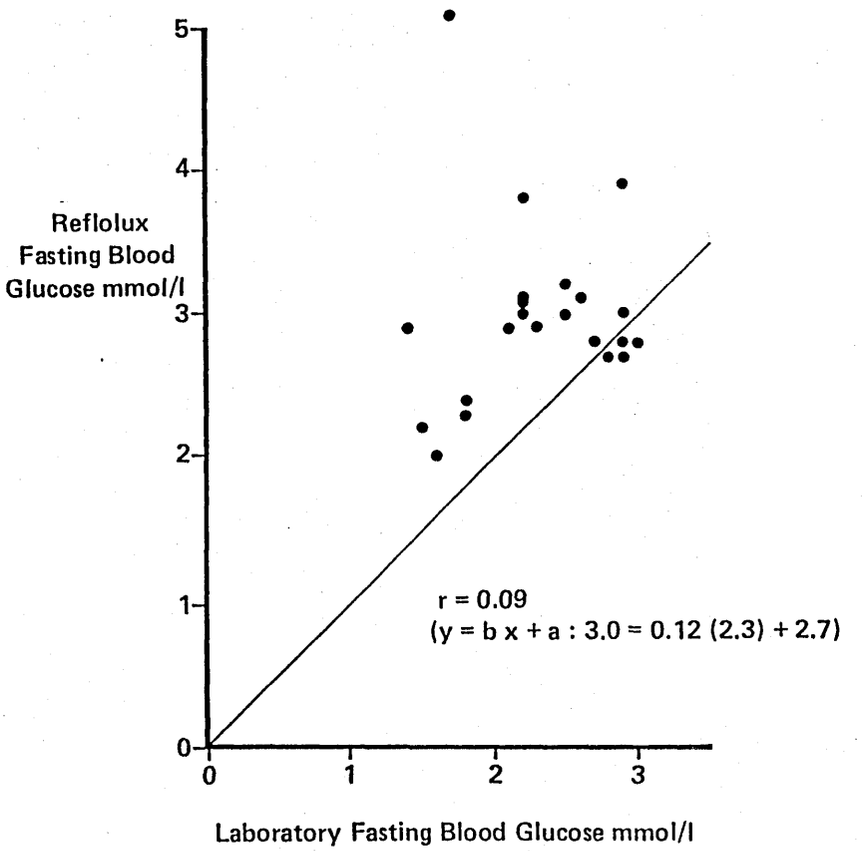


FIG. 20b Correlation between Reflolux and Yellow Springs fasting blood glucose levels, levels within the hypoglycaemic range.

TABLE 41

Differences in patient and laboratory glycaemic measures derived from monthly blood glucose filter paper card data in patients randomised to blood glucose testing.

MONTH AFTER RANDOMISATION	NUMBER OF PATIENT SAMPLES	FASTING BLOOD GLUCOSE (mmol/l)		MEAN BLOOD GLUCOSE (mmol/l)		M VALUE (UNITS)	
		LAB	PATIENT	LAB	PATIENT	LAB	PATIENT
1	51	6.8 (0.6)	7.4 (0.5)	7.6 (0.3)	8.4 (0.2)	30 (5)	39 (4)
2	53	6.5 (0.5)	7.1 (0.4)	7.9 (0.4)	8.9 (0.4)	33 (6)	51 (6)
3	46	6.9 (0.5)	8.2 (0.5)	7.4 (0.4)	8.8 (0.4)	29 (6)	44 (6)
4	50	6.5 (0.5)	7.9 (0.5)	7.3 (0.4)	9.0 (0.3)	28 (6)	48 (6)
5	46	6.0 (0.5)	7.2 (0.5)	7.0 (0.4)	8.6 (0.3)	23 (5)	44 (5)
6	48	6.2 (0.5)	7.3 (0.4)	7.0 (0.3)	8.4 (0.3)	23 (4)	38 (5)
7	42	6.7 (0.7)	7.1 (0.4)	6.6 (0.3)	8.7 (0.3)	14 (5)	42 (5)
8	51	6.5 (0.6)	7.8 (0.5)	6.7 (0.4)	8.6 (0.3)	20 (6)	41 (5)
9	51	6.4 (0.5)	7.5 (0.3)	7.1 (0.4)	8.8 (0.3)	24 (5)	45 (5)
10	49	5.9 (0.4)	7.5 (0.5)	6.9 (0.4)	9.0 (0.4)	15 (4)	47 (5)
11	45	5.8 (0.4)	7.8 (0.4)	6.2 (0.3)	8.2 (0.3)	8 (5)	34 (6)
12	52	6.1 (0.4)	7.8 (0.4)	6.4 (0.2)	8.2 (0.3)	13 (3)	33 (4)

Figures are mean (SEM). All comparisons lab. v. patient $p<0.01$.

during the first year of the study and were asked to complete a monthly 10 point filter card spot blood glucose profile and record their own blood glucose values recorded simultaneously on the Reflolux meter.

55 individuals provided information during the first year. Of a maximum of 120 paired blood spots and patient results, the average number (mean (SEM)) suitable for analysis over the year was 94 (4) per person. Only 10 patients provided 120 spots for analysis. Patient recorded results were generally higher then laboratory measured filter card blood glucose values. On average 62.2 (2.8)% mean (SEM) of patients blood glucose recordings deviated by at least 20% more then the laboratory values. The month by month differences in patient and laboratory glycaemic measures are shown in table 41. In addition to clear differences throughout the year, there was no suggestion of a trend towards an improved correlation with time between patient and laboratory results, with patient mean blood glucose results roughly 1 mmol/l higher.

CHAPTER 4

ASPECTS OF LIPID METABOLISM

1:1 FASTING LIPIDS AND LIPOPROTEINS IN INSULIN-DEPENDENT DIABETIC MEN WITHOUT CLINICAL NEPHROPATHY

Subjects: Of the 99 males recruited to the study, 57 with insulin dependent diabetes mellitus (IDDM) (previous ketoacidosis in 80% of cases) were matched with a group of 81 healthy male factory workers with no history of diabetes mellitus, who had been studied on a separate occassion by Dr. Paul Durrington at the Manchester Royal Infirmary. All subjects were aged between 35 and 70 years. The two groups were of similar social backgrounds and came from the adjacent districts of Old Trafford and Salford within Greater Manchester. None of the subjects were taking drugs known to affect levels of serum lipids and lipoproteins other than insulin or had any other disease which might affect lipid and lipoprotein metabolism.

In the group of men with IDDM, renal function was well preserved (serum creatinine less than 140 µmol/L and proteinuria less than 0.3 g/L). Glycaemic control in the diabetic men was suboptimal but was not poor (HbA_1 9.1 $\pm$ 1.7% (mean $\pm$ SD); fasting blood glucose 11.1 $\pm$ 6.4 mmol/L, mean blood glucose 12.6 $\pm$ 3.7 mmol/L).

Results : Clinical and lipid and lipoprotein data on the two groups are shown in Tables 42 and 43. Total serum and LDL cholesterol levels tended to be lower in the diabetic men than the healthy controls, but the differences were not significant. However the serum concentration of apolipoprotein B, the major protein component of LDL, was significantly lower in the diabetic men than in the controls.

Serum triglyceride and HDL and HDL_2 cholesterol levels were

slightly but not significantly higher in the diabetic men. Levels of HDL_3 cholesterol, and the ratios of HDL to LDL cholesterol and of HDL to total serum cholesterol, were significantly higher in the diabetic population.

Table 42 CLINICAL DATA FOR HEALTHY MALE CONTROLS AND MALE IDDM PATIENTS

	HEALTHY CONTROLS	IDDM PATIENTS
NUMBER	81	57
AGE (YEARS)	49.6 (6.6)	49.8 (9.5)
QUETELET'S INDEX (B.M.I.)	25.6 (2.9)	24.0 (2.9)
ALCOHOL DRINKERS (%)	88	75
ALCOHOL CONSUMPTION c(g/WEEK)	98 (0 - 810)	102 (0 - 700)
SMOKERS (%) *	22	30
STRENUOUS EXERCISE (%)	25	28
SYSTOLIC BLOOD PRESSURE (mmHg)	133 (19)	142 (20)
DIASTOLIC BLOOD PRESSURE (mmHg)	82 (12)	80 (12)

Figure are mean (SD), median (range) or as stated.

* greater than 10 cigarettes a day.

Table 43 SERUM LIPIDS AND LIPOPROTEINS IN HEALTHY MALE CONTROLS AND MALE IDDM PATIENTS

	HEALTHY CONTROLS	IDDM PATIENTS
SERUM TRIGLYCERIDES (mmol/L)	1.30 (1.15-1.49)	1.52 (1.31-1.78)
TOTAL SERUM CHOLESTEROL (mmol/L)	6.34 (1.14)	5.88 (1.53)
LDL CHOLESTEROL (mmol/L)	4.31 (1.21)	4.06 (1.14)
APOLIPOPROTEIN B (mg/dl) ***	137 (29)	103 (32)
HDL CHOLESTEROL (mmol/L)	1.36 (0.32)	1.45 (0.36)
HDL_2 CHOLESTEROL (mmol/L)	0.73 (0.32)	0.67 (0.31)
HDL_3 CHOLESTEROL (mmol/L) ***	0.63 (0.20)	0.78 (0.24)
LDL $\frac{\text{CHOLESTEROL}}{\text{APO B}}$ + ***	1.18 (0.40)	1.61 (0.59)
$\frac{\text{HDL CHOLESTEROL}}{\text{TOTAL}}$ **	0.21 (0.07)	0.26 (0.08)
$\frac{\text{HDL CHOLESTEROL}}{\text{LDL}}$ *	0.33 (0.15)	0.41 (0.22)

Figures are mean (SD) or geometric mean (95% confidence limits)
+ MASS RATIO (1 mmol/L LDL CHOLESTEROL = 39 mg/dl)

* $p<0.05$
** $p<0.002$
*** $p<0.001$

1:2. FASTING LIPIDS AND LIPOPROTEINS AND VASCULAR DISEASE IN IDDM WITH AND WITHOUT EARLY CLINICAL NEPHROPATHY

Subjects : 205 insulin-dependent diabetics (the 153 recruited to the trial and the 52 controls) were evaluated, from whom I identified 22 individuals (20 men) with early clinical nephropathy (persistent proteinuria >0.5g/day) in whom creatinine clearance was well preserved (>40 ml/min/1.73m^2). These 22 patients were matched in order of importance for sex, age, duration of diabetes (to within 5 years except in 3 cases), and HbA_1 (to within 1% except in 1 case) with 22 insulin-dependent diabetics out of 140 with normal albumin excretion rates. The urinary protein output and albumin excretion rates of those with clinical nephropathy were 1.35 (0.4-4.5) g/24 hours (geometric mean (range)) and 452.5 (213.0-961.4) µg/min, respectively, whereas the corresponding values for those with normal albumin excretion rates were 0.1 (0.05-0.3)g/24 hours and 5.3 (2.9-9.6)µg/min. All patients with clinical diabetic nephropathy had been diabetic for at least 7 years, with persisent proteinuria for a minimum of 6 months, and none had any history or findings suggestive of non-diabetic renal disease. All the subjects in the study were considered to be insulin-dependent and 84% had experienced at least one previous documented episode of ketoacidosis. None of the subjects was taking drugs other than insulin at the time of assessment which might affect lipoprotein metabolism or renal function. No specific advice regarding the dietary content of fat, fibre or protein had been given at the time of assessment.

Table 44 CHARACTERISTICS OF INSULIN DEPENDENT DIABETICS WITH NORMAL ALBUMIN EXCRETION RATE OR PROTEINURIA.

	NORMAL ALBUMIN EXCRETION RATE IDDM	PROTEINURIA IDDM
NUMBER (SEX) OF PATIENTS	22 (20M,2F)	22 (20M,2F)
AGE (YEARS)	44.2 (13.6)	43.7 (13.7)
AGE AT ONSET OF DIABETES (YEARS)	25.2 (13.6)	23.8 (14.4)
DURATION OF DIABETES (YEARS)	19.1 (8.4)	20.0 (8.5)
BODY MASS (QUETELET'S) INDEX	24.1 (3.3)	25.1 (3.7)
INSULIN DOSE (UNITS/DAY)	51 (14)	56 (18)
NO. OF SMOKERS	6.	8.
WEEKLY ALCOHOL CONSUMPTION (g)	48 (0-240)	64 (0-640)
FASTING BLOOD GLUCOSE (mmol/L)	11.4 (3.0-26.7)	9.6 (1.3-24.5)
HbA_1 (%)	8.9 (1.5)	8.7 (1.0)
SERUM UREA (mmol/L)	5.6 (1.5)	7.2 (2.5) **
SERUM CREATININE (µmol/L)	91 (12)	112 (30) *
CREATININE CLEARANCE (ml/min/1.73 m2)	105 (29)	92 (34)
SERUM ALBUMIN (g/l)	43 (2)	42 (3)

Figures are mean (SD), median (range) or as stated

* $p<0.05$ ** $p<0.02$

Table 45.

CLINICAL FEATURES OF INSULIN-DEPENDENT DIABETICS WITH NORMAL ALBUMIN EXCRETION OR WITH PROTEINURIA

	NORMAL ALBUMIN EXCRETION RATE	PROTEINURIA
MACROVASCULAR DISEASE (EITHER ISCHAEMIC HEART) (DISEASE AND/OR PERIPHERAL) (VASCULAR DISEASE)	3	10. *
ISCHAEMIC HEART DISEASE	2	8 *
PERIPHERAL VASCULAR DISEASE	2	8 *
BACKGROUND RETINOPATHY	11	4 *
PROLIFERATIVE RETINOPATHY	4	11 *
SYSTOLIC BLOOD PRESSURE (mmHg) $	135 (19)	161 (18)***
DIASTOLIC BLOOD PRESSURE (mmHg) £	79 (15)	90 (12)**

Figures are NUMBER, OR MEAN (SD)

$ 95% CONFIDENCE INTERVAL OF DIFFERENCE BETWEEN MEANS 15 TO 38 mmHg.

£ 95% CONFIDENCE INTERVAL OF DIFFERENCE BETWEEN MEANS 3 TO 19 mmHg

* $p<0.05$ ** $p<0.02$ *** $p<0.0001$

Results: The groups with proteinuria and normal albumin excretion rates were similar with regard to age, age at onset and duration of diabetes, body mass (Quetelet's) index, and daily insulin dosage. There was no excess of smokers or difference in alcohol consumption in those with proteinuria, and glycaemic control and serum albumin concentrations were comparable in both groups. Patients with proteinuria had on average moderately increased serum urea ($p<0.02$) and creatinine ($p<0.05$) concentrations, although their corrected creatinine clearance was not reduced significantly. (Table 44). Macrovascular disease (ischaemic heart disease, peripheral vascular disease, or both) was significantly more prevalent in diabetics with proteinuria ($p<0.05$). Although retinopathy was present in 15 patients in each group, proliferative features were more frequent in those with proteinuria ($p<0.05$). Systolic and diastolic blood pressures were higher in the patients with proteinuria ($p<0.0001$ and $p<0.02$ respectively). (Table 45).

Concentrations of serum cholesterol, triglycerides, LDL cholesterol, apolipoprotein B, and the mass ratio of LDL cholesterol to apolipoprotein B tended to be higher in patients with proteinuria, but without reaching levels of significance, though the increased total serum cholesterol was close ($p<0.1$; 95% confidence interval - 0.39 to 1.20 mmol/l). Total HDL cholesterol concentrations did not differ significantly when isolated by ultracentrifugation, but the value was decreased in patients with proteinuria when precipitation was used ($p = 0.03$). There was also a significant reduction in the concentration of cholesterol in the HDL_2 subfraction determined by

ultracentrifugation ($p = 0.03$), with a suggestively higher concentration of cholesterol within the HDL_3 subfraction ($p = 0.08$; 95% confidence interval - 0.01 to 0.23 mmol/l) in patients with proteinuria. (Table 46).

Table 46

LIPIDS AND LIPOPROTEINS IN INSULIN-DEPENDENT DIABETICS WITH NORMAL ALBUMIN EXCRETION RATE OR WITH PROTEINURIA

	NORMAL ALBUMIN EXCRETION RATE	PROTEINURIA
TRIGLYCERIDES (mmol/l)	1.27 (0.68-2.39)	1.42 (0.81-2.70)
CHOLESTEROL (mmol/l)$	5.51 (1.25)	6.13 (1.44)
LDL CHOLESTEROL (mmol/l)	3.39 (1.17)	3.84 (1.52)
APOLIPOPROTEIN B (mg/dl)	107.1 (36.1)	111.1 (31.6)
LDL CHOLESTEROL (*) / APOLIPOPROTEIN B	1.31 (0.49)	1.42 (0.62)
HDL uc CHOLESTEROL (mmol/l)	1.49 (0.39)	1.38 (0.26)
HDL pt CHOLESTEROL £ (mmol/l)	1.46 (0.37)	1.24 (0.25) **
HDL_3 uc CHOLESTEROL (mmol/l) @	0.69 (0.21)	0.79 (0.22)
HDL_2 uc CHOLESTEROL (mmol/l) +	0.80 (0.35)	0.59 (0.27) **
HDL uc CHOLESTEROL / LDL uc	0.50 (0.23)	0.42 (0.20)

Figures are geometric mean (range) or mean (SD) ** p = 0.03

uc Refers to ultracentrifugation data
pt Refers to precipitation data

(*) LDL CHOLESTEROL CONVERTED TO mg/dl (x39) FOR CALCULATION OF RATIO

$ 95% CONFIDENCE INTERVAL - 0.39 TO 1.20 mmol/l
£ 95% CONFIDENCE INTERVAL 0.02 TO 0.41 mmol/l
@ 95% CONFIDENCE INTERVAL - 0.01 TO 0.23 mmol/l
+ 95% CONFIDENCE INTERVAL 0.02 TO 0.40 mmol/l

1:3. PREVALENCE OF HYPERLIPIDAEMIA AND RELATED CLINICAL FEATURES

Subjects: 205 insulin-dependent diabetic aged 16-70 (126M, 79F) were studied. All had well preserved renal function with normal serum creatinine levels except in 3 cases (153,154 and 156 μmol/l). I also compared the prevalence of hyperlipidaemia in the 81 healthy male factory workers with no history of diabetes mellitus with 81 insulin-dependent diabetic men of similar age range (35-70 years old).

Results: 55 (27%) of cases had fasting hypercholesterolaemia (>6.5 mmol/l), whilst 44 (21%) had fasting hypertriglyceridaemia (>2.25 mmol/l). Altogether, 40% (82) of the subjects with IDDM had hyperlipidaemia.

When 81 healthy control males matched for age were compared with 81 men with IDDM, body mass index, frequency of exercise and consumption of tobacco and alcohol did not differ between the two groups. Hypertriglyceridaemia was more prevalent in IDDM ($p<0.05$) and combined hyperlipidaemia marginally more common, whilst hypercholesterolaemia was if anything less common (Table 47).

The 205 individuals with IDDM were grouped according to whether they had normolipidaemia, combined hyperlipidaemia or hypercholesterolaemia or hypertriglyceridaemia alone. No differences were noted between the groups regarding sex ratio, body mass index or patterns of alcohol and tobacco consumption. Normolipidaemic patients were younger at the time of the study ($p = 0.03$) and at the age when diabetes was diagnosed ($p = 0.012$), and had lower levels of systolic ($p = 0.01$) and diastolic blood pressure ($p<0.05$), in comparison to the hypertriglyceridaemic

Table 47

PREVALENCE OF HYPERLIPIDAEMIA AND RELATED CLINICAL FEATURES IN 81 INSULIN-DEPENDENT DIABETIC AND 81 HEALTHY CONTROL MALES

	INSULIN DEPENDENT DIABETIC MEN	HEALTHY CONTROLS
NUMBER	81	81
AGE (YEARS)	49.4 (6.0)	49.6 (6.6)
BODY MASS INDEX	25.1 (2.1)	25.6 (2.9)
SMOKERS (%)	28	22
STRENUOUS EXERCISE (%)	29	25
ALCOHOL CONSUMPTION (g/WEEK)	100 (0-750)	98 (0-810)
PREVALENCE OF HYPERCHOLESTEROLAEMIA (NUMBER(%))	25 (30.9%)	36 (44%)
PREVALENCE OF HYPERTRIGLYCERIDAEMIA (NUMBER (%))	23 (28.4 %)	11 (13.6 %) *
PREVALENCE OF COMBINED HYPERTRIGLYCERIDAEMIA & HYPERCHOLESTEROLAEMIA (NUMBER (%))	10 (12.3 %)	5 (6.1 %)

Figures are as stated, median (range) or mean (SD)

* $p<0.05$

group. The daily insulin dose was greater in the combined hyperlipidaemic group in comparison to normolipidaemic and hypercholesterolaemic patients ($p<0.05$) (Table 48).

Levels of HbA_1 did not differ significantly, although fasting blood glucose levels in the group with combined hyperlipidaemia were greater than the other groups ($p<0.002$). Serum urea levels were comparable, but serum creatinine levels were lowest in normolipidaemic patients ($p = 0.03$), and total urinary protein excretion tended to be higher in patients with combined hyperlipidaemia ($p<0.06$) (Table 49).

Total triglyceride and cholesterol levels were highest in the group with combined hyperlipidaemia, indicating that when marked hypercholesterolaemia does occur in IDDM, it is almost invariably accompanied by hypertriglyceridaemia. Levels of LDL cholesterol, apolipoprotein B and the ratio of LDL cholesterol to apo B were significantly less in patients with normal lipid levels and hypertriglyceridaemia compared to the other groups ($p< 0.001$). HDL and HDL_2 cholesterol levels were least in the hypertriglyceridaemic group ($p = 0.05$ and $p = 0.02$ respectively), but levels of HDL_3 cholesterol did not differ between groups. The ratios of HDL/LDL and HDL/total cholesterol were greatest in the normolipidaemic patients and least in those with combined hyperlipidaemia ($p<0.0001$) (Table 50).

The cumulative frequency distributions of triglyceride and cholesterol levels are shown in Figures 21a and 21b. Multivariate analysis including insulin dosage, age at diagnosis of diabetes, age, body mass index, HbA_1, fasting blood glucose,

TABLE 48

Clinical Features in Normolipidaemic and Hyperlipidaemic Groups

	NORMOLIPIDAEMIA	HYPERCHOLESTEROLAEMIA ONLY	HYPERTRIGLYCERIDAEMIA ONLY	COMBINED HYPERLIPIDAEMIA
Number	123	37	27	18
Sex Ratio (M:F)	72:51	22:15	21:6	12:6
Age (years)	39(1)*	46(2)	43(3)	46(3)
Age at diagnosis of diabetes (years)	25(1)**	31(2)	32(3)	28(3)
Body Mass Index	23.7 (0.3)	25.0 (0.6)	25.4 (0.8)	24.7 (0.9)
Insulin dose (U/day)	49(1)$^{+2}$	49(3)	54(5)	59(5)
Alcohol consumption (g/week)	56 (0-400)	58 (0-250)	60 (10-500)	70 (5-740)
% of smokers	43.4	45.9	63.0	55.6
Systolic blood pressure (mmHg)	132 (2)$^{++}$	141 (4)	145 (4)	142 (8)
Diastolic blood pressure (mmHg)	75 (1)$^{+1}$	79 (2)	82 (3)	81 (3)

Clinical features of normolipidaemic and hyperlipidaemic subjects with IDDM. Figures are mean (SEM), % or number. * $p = 0.013$ Normolipidaemic v hypercholesterolaemic and combined hyperlipidaemic. ** $p = 0.012$ Normolipidaemic v hypercholesterolaemic and hypertriglyceridaemic. $^{++}$ $p = 0.01$ Normolipidaemic v hypertriglyceridaemic. $^{+1}$ $p < 0.05$ Normolipidaemic v hypertriglyceridaemic. $^{+2}$ $p < 0.05$ Normolipidaemic v combined hyperlipidaemic

TABLE 49

Glycaemic Control and Renal Function in Normolipidaemic and Hyperlipidaemic Groups with IDDM

	NORMOLIPIDAEMIA	HYPERCHOLESTEROLAEMIA ONLY	HYPERTRIGLYCERIDAEMIA ONLY	COMBINED HYPERLIPIDAEMIA
Fasting blood glucose (mmol/l)	9.9 (0.5)	9.9 (0.9)	11.8 (1.1)	15.1 (1.4)*
HbA_1 (%)	9.2 (0.2)	9.3 (0.4)	9.6 (0.4)	10.0 (0.3)
Serum Urea (mmol/l)	5.2 (0.1)	5.8 (0.3)	5.9 (0.4)	5.6 (0.3)
Serum creatinine (μmol/l)	80 (2)+	89 (4)	90 (4)	88 (5)
Total urinary protein (g/24 hours)	0.21 (0.05-2.70)	0.19 (0.05-4.50)	0.22 (0.10-4.20)	0.35 (0.05-5.30)Δ

Glycaemic control and renal function in normolipidaemic and hyperlipidaemic subjects with IDDM. Figures are mean (SEM) or median (range). * $p < 0.002$ Combined hyperlipidaemic different from all other groups. + $p = 0.03$ Normolipidaemic different from all other groups. Δ $p < 0.06$ Combined hyperlipidaemic different from normolipidaemic

TABLE 50

Lipids and Lipoproteins in Normolipidaemic and Hyperlipidaemic Groups with IDDM

	NORMOLIPIDAEMIA	HYPERCHOLESTEROLAEMIA ONLY	HYPERTRIGLYCERIDAEMIA ONLY	COMBINED HYPERLIPIDAEMIA
Number	122	37	27	18
Total triglycerides (nmol/l)	1.01 (0.39-2.24)	1.34 (0.36-2.24)	2.89 (2.29-4.59)	3.04 (2.34-23.29)
Total serum cholesterol (mmol/l)	4.97 (0.08)	7.41 (0.15)	5.42 (0.16)	7.98 (0.27)
LDL cholesterol (mmol/l)	3.11 (0.08)**1	5.38 (0.20)	3.09 (0.18)**1	5.34 (0.30)
Apolipoprotein B (mg/dL)	97.7 (2.2)**2	119.5 (5.7)	111.7 (5.5)**2	135.8 (9.9)
LDL $\frac{\text{cholesterol}}{\text{Apolipoprotein B}}$	1.29 (0.04)**1	1.87 (0.11)	1.14 (0.08)**1	1.62 (0.11)
HDL cholesterol (mmol/l)	1.45 (0.03)	1.57 (0.06)	1.26 (0.06)	1.45 (0.09)
HDL_2 cholesterol (mmol/l)	0.74 (0.03)	0.78 (0.06)	0.56 (0.04)	0.65 (0.05)
HDL_3 cholesterol (mmol/l)	0.72 (0.02)	0.79 (0.05)	0.70 (0.05)	0.78 (0.06)
$\frac{\text{HDL}}{\text{LDL}}$ cholesterol	0.47 (0.02)**1	0.29 (0.02)	0.41 (0.04)**1	0.27 (0.03)
$\frac{\text{HDL}}{\text{TOTAL}}$ cholesterol	0.29 (0.01)**2	0.21 (0.01)	0.23 (0.01)**2	0.18 (0.01)

Lipids and lipoproteins in normolipidaemic and hyperlipidaemic subjects with IDDM. Figures are mean (SEM) or median (range). **1 $p < 0.0001$ Normolipidaemic and hypertriglyceridaemic different from hypercholesterolaemic and combined hyperlipidaemic. **2 $p < 0.0001$ Normolipidaemic different from all other groups. Hyperlipidaemic different from combined hyperlipidaemic. + $p = 0.008$ Hypertriglyceridaemic different from normolipidaemic and hypercholesterolaemic. * $p = 0.02$ Hypertriglyceridaemic different from normolipidaemic and hypercholesterolaemic

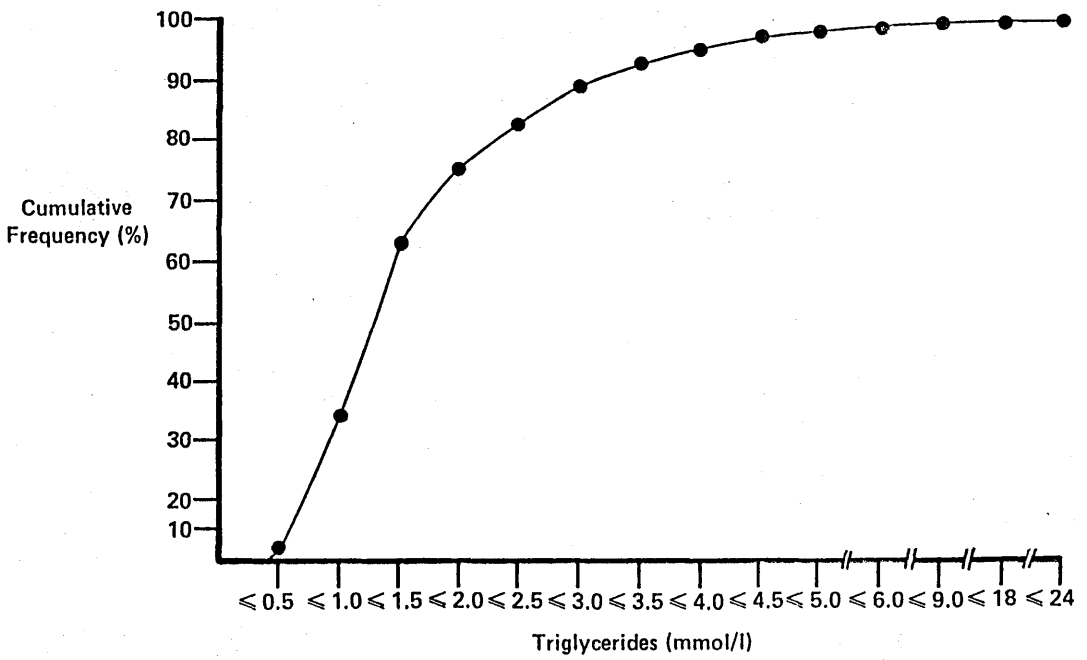


FIG. 21a Cumulative frequency of triglyceride data for 205 subjects with IDDM

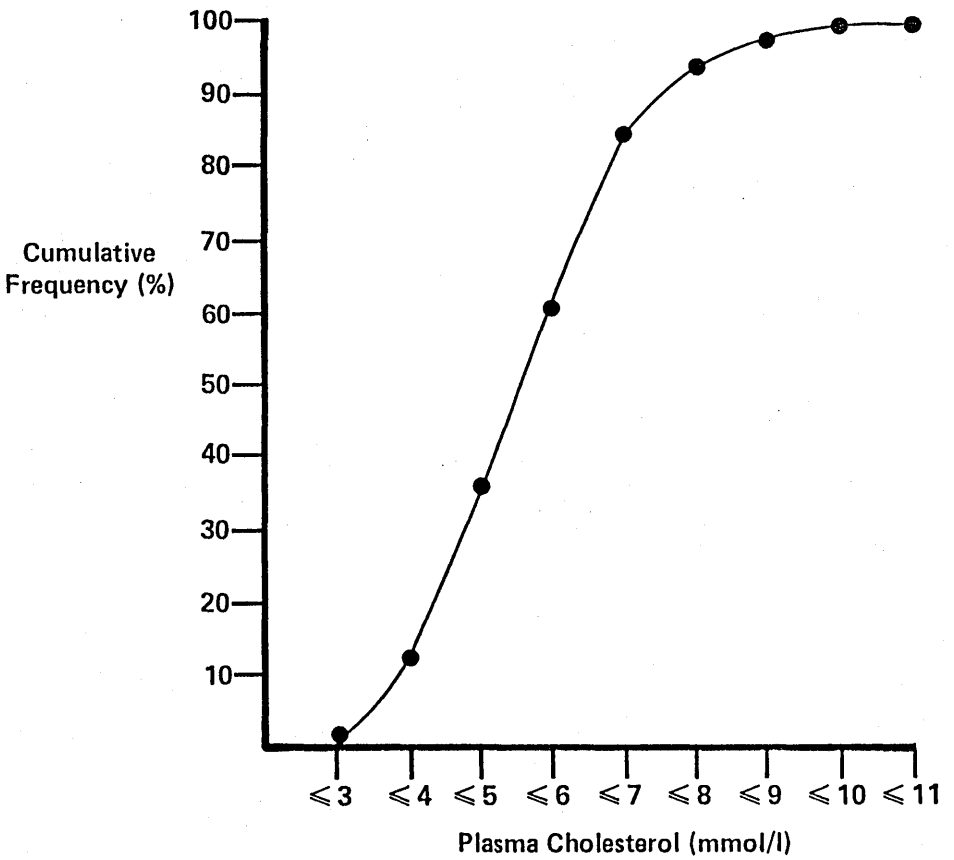


FIG. 21b Cumulative frequency of cholesterol data for 205 subjects with IDDM

alcohol and smoking habits and urinary protein excretion as co-variables showed that the most significant predictors of levels of triglycerides in IDDM were insulin dosage, age at diagnosis, HbA_1 and body mass index, whilst cholesterol levels were predicted by the age at the time of study, body mass index, urinary protein excretion, fasting blood glucose and HbA_1 levels (Table 51). Of these the most substantial contribution (partial regression coefficient) was provided by HbA_1 in the case of serum triglycerides, and proteinuria in the case of cholesterol.

Discussion: Although I was able to demonstrate hyperlipidaemia in 40% of cases, only hypertriglyceridaemia appeared to be commoner than in the non-diabetic population. Hyperlipidaemia in IDDM was independently associated with ageing, early renal dysfunction, higher daily insulin requirements, obesity and poorer glycaemic control.

The cut off levels for fasting hyperlipidaemia are arbitrary but the levels beyond which a benefit from treatment of hyperlipidaemia is considered probable in non-diabetics (737-739).

In support of the previous observation of increased cholesterol levels in early diabetic nephropathy, serum cholesterol was independently associated not only with protein excretion, but also with serum creatinine levels in patients with stable glomerular filtration function, confirming the importance of the kidney in lipid metabolism in IDDM.

TABLE 51

Predictor Variables for Triglycerides in IDDM

	Variable	Partial Regression Coefficient	Cumulative Regression Coefficient	Cumulative p
Triglyceride =	1. Daily insulin dose	0.029	0.26	< 0.0001
	2. Age at diagnosis of diabetes	0.031	0.35	= 0.001
	3. HbA_1	0.129	0.37	= 0.072
	4. Body mass index	0.064	0.39	= 0.074

Predictor Variables for Cholesterol in IDDM

	Variable	Partial Regression Coefficient	Cumulative Regression Coefficient	Cumulative p
Cholesterol =	1. Age	0.024	0.27	< 0.0001
	2. Body mass index	0.078	0.34	= 0.003
	3. Urinary protein excretion	0.319	0.37	= 0.019
	4. Fasting blood glucose	0.031	0.43	= 0.029
	5. HbA_1	0.096	0.44	= 0.087

Linear regression analysis of factors predictive of triglyceride and cholesterol levels in IDDM. Triglycerides multiple $r = 0.39$, $p < 0.0001$. Cholesterol multiple $r = 0.44$, $p < 0.0001$.

Triglyceride levels appeared more conspicuously associated with diabetic glycaemic control than cholesterol levels, and the latter tended to be elevated in conjunction with hypertriglyceridaemia. The higher daily insulin requirements in such cases of combined hyperlipidaemia might suggest a greater degree of insulin resistance in addition to less stable metabolic control in these patients. It was also of interest to find an association with renal dysfunction and combined hyperlipidaemia since this subpopulation with IDDM are at great risk for vascular disease (560), and appear similar in both these respects to individuals with type III hyperlipoproteinaemia.

Finally, HDL_2 cholesterol levels were reduced in these patients with hypertriglyceridaemia, although since the total HDL concentration in IDDM is often high, levels remained in the normal range for the non-diabetic population.

1:4. THE EFFECT OF APOLIPOPROTEIN E POLYMORPHISM ON LIPIDS AND LIPOPROTEINS

Subjects: Of the 205 patients, apolipoprotein E phenotyping was carried out on 120 (71M,49F), aged 15 - 72 years. Their duration of diabetes varied from 8 months to 42 years. 63% had no detectable C-peptide response to a mixed meal, and more than 80% had experienced at least one episode of diabetic ketoacidosis. All had reasonable glycaemic control when assessed (HbA_1 9.5 $\pm$ 1.5% (mean $\pm$ SD)).

None had evidence of hepatic disease or of advanced nephropathy (serum creatinine less than 140 µmol/l except 2 cases (153 and 186 µmol/l). None were on medication which could affect lipid metabolism at the time of assessment other than insulin. The expected prevalences of the different apo E phenotypes based on gene frequency were determined according to Hardy-Weinberg equilibrium and compared with those observed. Absolute probabilities of the lowest three frequencies were compared using the t-test for the normal approximation to binomial distribution.

Results: Five of the six potential apo E phenotypes were identified. Although gene frequencies were similar to non-diabetic populations, a clear excess of the Apo E2/E2 phenotype (6.7%) was observed when compared to the prevalence of 0-2% described in non-diabetic populations. Prevalences of E2/E2 homozygosity and E2/E3 heterozygosity were significantly different from those expected according to Hardy-Weinberg equilibrium ($p<0.0002$ and $p<0.005$ respectively). The reported prevalences of the other phenotypes did not differ from those

predicted (Table 52). No significant differences were found between the five groups with regard to age, body mass index, daily insulin dosage, glycaemic control, serum creatinine and urinary protein excretion. However in the apoE2/E2 group, duration of diabetes was less ($p = 0.01$) and C-peptide reserve was significantly greater ($p = 0.025$) than in the others (Table 53).

Table 52

Apo E PHENOTYPE PREVALENCE AND GENE FREQUENCY IN 120 INSULIN TREATED DIABETICS

	E2/2	E2/3	E3/3	E3/4	E4/4	E2/4
Observed Number	8**	6*	79	23	4	0
%	6.7	5.0	65.8	19.2	3.3	0.0
Expected Number	1	17	73	24	2	3
%	0.8	14.2	60.8	20.2	1.7	2.3

Gene Frequency

$\epsilon 2$ 0.091

$\epsilon 3$ 0.780

$\epsilon 4$ 0.129

*P<0.005 **P<0.0002 different from expected prevalence according to Hardy-Weinberg equilibrium

Table 53

CLINICAL AND BIOCHEMICAL FEATURES OF 120 INSULIN-TREATED DIABETICS GROUPED ACCORDING TO Apo E PHENOTYPE

	E2/2	E2/3	E3/3	E3/4	E4/4
SEX M:F	6:2	4:2	46:33	14:9	1:3
AGE (years)	43(3)	42(8)	42(2)	42(3)	41(9)
BODY MASS INDEX	28(2)	27(2)	24(1)	24(1)	24(2)
DURATION OF DIABETES (yrs)*	7(1)	12(1)	13(1)	19(2)	23(9)
INSULIN DOSAGE (U/day)	50(9)	43(8)	49(2)	52(2)	35(6)
FASTING BLOOD GLUCOSE(mmol/L)	8.8(1.7)	14.9(2.3)	10.3(0.5)	12.3(1.3)	7.8(4.1)
MEAN BLOOD GLUCOSE (mmol/L)	11.0(1.3)	14.6(2.4)	12.6(0.6)	12.9(0.8)	12.5(6.3)
HbA_1 (%)	8.9(0.8)	8.6(0.9)	9.6(0.2)	9.7(0.4)	9.2(0.4)
C-PEPTIDE ** (pmol/L)	0.370 (0-2.50)	0.025 (0-0.77)	0.002 (0-1.90)	0.004 (0-0.70)	0.127 (0-0.760)
SERUM CREATININE (umol/L)	77(4)	96(12)	80(2)	91(5)	92(12)
URINARY PROTEIN (g/24 hrs)	0.35 (0.05-0.90)	0.40 (0.20-4.20)	0.21 (0.05-5.30)	0.30 (0.05-1.60)	0.45 (0.05-2.20)

Figures expressed are number, median (range) or mean (SEM)

Comparisons not significant unless: *p = 0.01, **p = 0.025

Results: Total serum cholesterol was lowest when the ϵ2 allele was present (E2 homozygotes and heterogyzotes), intermediate in E3 homozygotes and highest in those possessing an ϵ4 allele (E3/4 or E4/4) (p=0.038). LDL cholesterol was similarly distributed, with lowest levels observed in those with an ϵ2 allele and highest in those with an ϵ4 allele (p = 0.042). A similar non-significant (p= 0.1) trend was observed for apolipoprotein B. A tendency for HDL cholesterol levels to increase in parallel with LDL cholesterol was noted, due largely to HDL_3, which meant that despite the higher LDL in the group possessing an ϵ4 allele, their HDL to LDL and HDL to total cholesterol ratio tended to be lower (Table 54).

Of the 8 diabetics who were E2 homozygotes, only one was identified with classical type III hyperlipoproteinaemia with tuber-eruptive xanthomata, arcus senilis formation and peripheral vascular disease. Another individual had fasting hyperlipidaemia (cholesterol 8.50 mmol/L; triglycerides 4.58 mmol/l) with dysbetalipoproteinaemia (pre-beta and broad beta band on electrophoresis), but without stigmata of type III hyperlipoproteinaemia. The remaining six were all normolipidaemic without detectable pre-β banding on electrophoresis and without clinical features of type III hyperlipoproteinaemia.

Table 54

SERUM LIPIDS AND LIPOPROTEINS IN 120 INSULIN-TREATED DIABETICS GROUPED ACCORDING TO EXPRESSION OF ∈2,∈4 OR E3/3

	∈2	E3/3	∈4
TRIGLYCERIDES (mmol/L)	1.46 (0.46-23.29)	1.34 (0.36-5.40)	1.14 (0.49-3.50)
CHOLESTEROL * (mmol/L)	5.43(0.56)	5.61(0.16)	6.21(0.56)
LDL CHOLESTEROL ** (mmol/L)	3.07(0.41)	3.60(0.16)	4.02(0.52)
APOLIPOPROTEIN B (mg/DL)	97 (11)	106(3)	123(16)
LDL CHOLESTEROL / APOLIPOPROTEIN B	1.38(0.18)	1.36(0.06)	1.34(0.10)
HDL CHOLESTEROL (mmol/L)	1.37(0.11)	1.46(0.04)	1.48(0.14)
HDL_2 CHOLESTEROL (mmol/L)	0.69(0.12)	0.71(0.03)	0.72(0.14)
HDL_3 CHOLESTEROL (mmol/L)	0.68(0.12)	0.74(0.03)	0.77(0.13)
HDL/LDL CHOLESTEROL	0.50(0.06)	0.47(0.02)	0.42(0.04)
HDL/TOTAL CHOLESTEROL	0.27(0.03)	0.27(0.01)	0.25(0.02)

Figures expressed as median (range) or mean (SEM)

*p = 0.028, **p = 0.042

1:5 THE EFFECTS OF SHORT TERM IMPROVEMENTS IN METABOLIC CONTROL ON LIPIDS AND LIPOPROTEINS IN IDDM

In Chapter 3 I demonstrated that levels of total and LDL serum cholesterol and total triglycerides fell in response to intensification of management (Table 30). In view of the previous observations that hyperlipidaemia was present in 40% of all patients with IDDM that I examined (Chapter 4, 1:3), I investigated whether the bulk of the overall response in serum lipids took place in those with hyperlipidaemia.

I therefore looked in detail at changes in lipid and lipoprotein levels in the initial 147 subjects on whom data was available, who were classified according to whether they were normolipidaemic (cholesterol less than 6.5 mmol/l, triglycerides less than 2.25 mmol/l), hypercholesterolaemic only (cholesterol greater than 6.5 mmol/l, triglycerides less than 2.25 mmol/l), hypertriglyceridaemic only (cholesterol less than 6.5 mmol/l, triglycerides greater than 2.25 mmol/l) or had combined hyperlipidaemia (cholesterol greater than 6.5 mmol/l, triglycerides greater than 2.25 mmol/l). 57 of the initial 147 (39%) had hyperlipidaemia in one form or another, which is more or less the prevalence observed in the larger group of 205 which included diabetic controls who were not recruited to the home glucose monitoring study. Of these 57, 24 had hypercholesterolaemia, 19 had hypertriglyceridaemia and 14 had combined hyperlipidaemia. After the period of intensive management only 26 (19%) of the 137 subjects remained hyperlipidaemic. 12 had hypercholesterolaemia, 4 had hypertriglyceridaemia and 10 had combined hyperlipidaemia

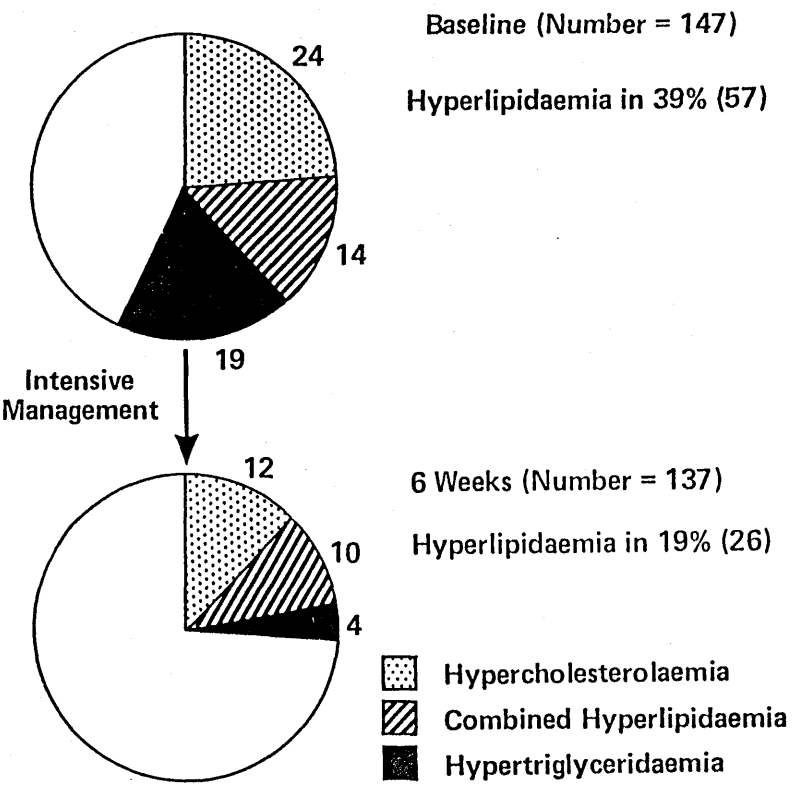


FIG. 22 The effect of intensification of management of the prevalence of hyperlipidaemia.

(Figure 22). The actual changes in lipids and lipoproteins in the patients were grouped according to their initial lipid status and are shown in Tables 55 and 56. Triglyceride levels remained unaltered in the normolipidaemic group, but fell in the other groups, particularly in those patients with hypertriglyceridaemia. On the other hand total and LDL cholesterol levels only fell significantly in those who were hypercholesterolaemic initially.

Apolipoprotein B and total HDL cholesterol levels essentially remained unaltered although a marked fall in both was observed in the group with combined hyperlipidaemia. However the most obvious changes were with regard to HDL cholesterol subfractions. HDL_2 cholesterol levels showed a definite rise in the hypercholesterolaemic group, whilst they fell in the combined hyperlipidaemic group and remained unaltered in the other 2 groups. In distinction HDL_3 cholesterol levels fell in all 4 groups.

TABLE 55

CHANGES IN LIPIDS DURING INTENSIVE MANAGEMENT PERIOD ACCORDING TO INITIAL LIPID STATUS

	NORMOLIPIDAEMIC	HYPERCHOLESTEROLAEMIC	HYPERTRIGLYCERIDAEMIC	COMBINED HYPERLIPIDAEMIA
Initial Number in each Group (Total 147)	90	24	19	14
Number in each Group after 6 weeks (Total 137)+	111	12	4	10
Fasting Triglycerides (mmol/l)				
Baseline	0.99 (0.39-2.14)	1.26 (0.36-2.14)	3.04 (2.29-5.49)	3.00 (2.26-23.29)
6 Weeks	0.99 (0.24-2.94)	1.14* (0.34-2.38)	1.64* (1.04-3.24)	1.85** (1.09-19.39)
Fasting Cholesterol (mmol/l)				
Baseline	4.93 (0.10)	7.42 (0.20)	5.22 (0.21)	7.88 (0.26)
6 Weeks	4.82 (0.12)	6.33 (0.35)***	5.00 (0.22)	6.45 (0.44)***

*p < 0.05 ***p < 0.001 changes from baseline. Figures are mean (SEM)

+6 of the normolipidaemic group had hyperlipidaemia after 6 weeks (3 with hypercholesterolaemia and 3 with combined hyperlipidaemia).

TABLE 56

CHANGES IN LIPOPROTEINS AND APOLIPOPROTEIN B DURING INTENSIVE MANAGEMENT PERIOD ACCORDING TO INITIAL LIPID STATUS

	NORMOLIPIDAEMIC	HYPERCHOLESTEROLAEMIC	HYPERTRIGLYCERIDAEMIC	COMBINED HYPERLIPIDAEMIA
LDL Cholesterol (mmol/l)				
Baseline	3.17 (0.10	5.55 (0.23)	3.12 (0.24)	5.31 (0.27)
6 Weeks	3.04 (0.11)	4.72 (0.19)***	3.30 (0.25)	4.12 (0.37)***
Apolipoprotein B (mg/dl)				
Baseline	95 (2)	110 (6)	108 (7)	134 (9)
6 Weeks	96 (3)	110 (5)	105 (6)	110 (6)***
HDL_{uc} Cholesterol (mmol/l)				
Baseline	1.48 (0.04)	1.57 (0.07)	1.27 (0.06)	1.43 (0.09)
6 Weeks	1.42 (0.03)	1.60 (0.12)	1.20 (0.08)	1.18 (0.10)***
HDL_{2uc} Cholesterol (mmol/l)				
Baseline	0.77 (0.03)	0.76 (0.09)	0.62 (0.05)	0.64 (0.05)
6 Weeks	0.78 (0.04)	0.91 (0.09)**	0.62 (0.07)	0.56 (0.09)*
HDL_{3uc} Cholesterol (mmol/l)				
Baseline	0.71 (0.03)	0.81 (0.06)	0.65 (0.06)	0.78 (0.06)
6 Weeks	0.64 (0.02)**	0.69 (0.06)**	0.58 (0.06)*	0.62 (0.06)

*$p < 0.05$ **$p < 0.01$ ***$p < 0.001$ changes from baseline. Figures are mean (SEM)

1:6 THE EFFECTS OF LONG TERM METABOLIC CONTROL ON LIPIDS AND LIPOPROTEINS IN IDDM

Lipid and lipoprotein levels differed little according to whether patients were carrying out blood or urine glucose testing (Chapter 3, 1:5). However in both groups lipid levels seemed to rise a little after 6 months in relation to their levels at 6 weeks, and thereafter fell. In order to assess this more closely I examined changes in lipids over this time with patients again categorized according to their initial lipid levels (Tables 57 and 58). In addition lipids and lipoprotein levels were compared for the study group as a whole with the 52 diabetic clinic controls, initially, and after 6 and 12 months (Figure 23).

In the normolipidaemic group mean levels of triglycerides and cholesterol remained unchanged throughout the year, despite the fact that hyperlipidaemia was observed in as many as 7 cases at 6 months and 1 year (Table 58). A sustained fall in total and LDL cholesterol was seen in both the hypercholesterolaemic and combined hyperlipidaemic groups at 6 months and 1 year; in addition triglyceride levels remained lower in the hypertriglyceridaemic and combined hyperlipidaemic levels throughout the year (Tables 57 & 58). The absolute number of subjects with hyperlipidaemia was roughly the same at 6 months and 1 year; and comparable although proportionately greater to the number after 6 weeks of intensified management. Over the whole year the maximum impact in reducing the number of hyperlipidaemic patients was seen in the hypertriglyceridaemic

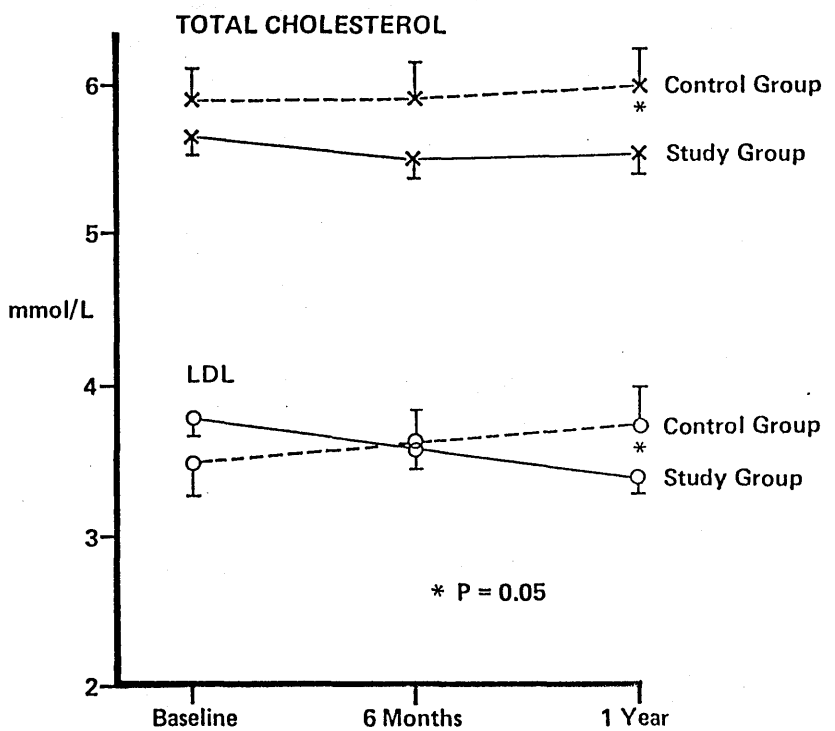


FIG 23 Total and LDL cholesterol levels in control and study groups over 1 year.

Figures represent Mean ± SEM

group and to a lesser extent in the hypercholesterolaemic group. The number of patients with combined hyperlipidaemia remained fairly constant, and 8 cases had persistant combined hyperlipidaemia during the study. Levels of apolipoprotein B and HDL cholesterol remained fairly stable in the 4 groups throughout the year. Likewise HDL cholesterol subfractions remained unaltered, with the notable exception of the combined hyperlipidaemic group, in whom HDL_2 cholesterol levels continued to fall (Table 58).

Total and LDL cholesterol levels for the study group as a whole were comparable to the diabetic controls initially and at 6 months, although LDL cholesterol levels tended to be lower after 1 year in the study group ($p = 0.05$) (Figure 23). Triglyceride levels were also comparable in both groups basally but remained at the levels seen after 6 weeks intensive management in the study group at 6 months and 1 year ($p<0.05$ in comparison to baseline). On the other hand levels remained fairly stable in the control group, so consequently the levels were significantly greater in the control group at 6 months and 1 year ($p<0.05$).

HDL cholesterol levels tended to be higher ($p = 0.05$) in the control groups (1.48(0.35), mean (SEM), mmol/l) than in the study group (1.39 (0.04) mmol/l) after 6 months but after 1 year levels of HDL cholesterol had risen in the study group (1.44 (0.04) mmol/l) approximating to those in the control group. HDL_2 cholesterol levels were indistinguishable between control and study groups during the year, and therefore it was HDL_3 cholesterol levels which changed most, with higher levels in the control group (0.77 (0.03) mmol/l) at 6 months in comparison to

the study group (0.70 (0.04) mmol/l) ($p< 0.05$). Again levels had risen somewhat by 1 year in the study group (0.75 (0.03) mmol/l) so the difference was no longer evident. Levels of apolipoprotein B remained stable in the control group throughout the year (119 (3) mg/dl at 6 months and 119 (3) mg/dl at 1 year), and consequently higher than the study population at these time points ($p<0.05$), although it should be pointed out that the control group also had higher apo B levels at the outset of the study.

TABLE 57

CHANGES IN SERUM LIPIDS AT 6 MONTHS AND 1 YEAR ACCORDING TO INITIAL LIPID STATUS

	NORMOLIPIDAEMIC	HYPERCHOLESTEROLAEMIC	HYPERTRIGLYCERIDAEMIC	COMBINED HYPERLIPIDAEMIA
Number of Patients				
Basal (Total 147)	90	24	19	14
6 Months (Total 124)	93	16	4	11
1 Year (Total 124)	95	11	4	14
Cholesterol (mmol/l)				
Basal	4.93 (0.10)	7.42 (0.20)*	5.22 (0.21)	7.88 (0.26)*
6 Months Δ	5.08 (0.12)	6.88 (0.29)	5.02 (0.14)	6.07 (0.37)
1 Year +	4.98 (0.12)	6.79 (0.27)	5.38 (0.22)	6.72 (0.49)
Triglycerides (mmol/l)				
Basal	0.99 (0.39-2.14)	1.26 (0.36-2.14)	3.04** (2.29-4.59)	3.00* (2.22-23.29)
6 Months Δ	0.95 (0.19-3.04)	1.22 (0.69-2.84)	1.59 (0.64-3.74)	2.14 (1.14-58.90)
1 Year +	1.05 (0.29-3.04)	1.29 (0.64-8.90)	1.44 (0.54-4.79)	2.29 (0.69-11.89)

Δ After 6 months 31 patients had hyperlipidaemia. + After 1 year 29 patients had hyperlipidaemia.

Hypercholesterolaemia was present at 6 months and 1 year in 7 of the subjects who were originally normocholesterolaemic, whilst hypertriglyceridaemia was present in 2-3 cases at 6 months and 1 year.

*$p < 0.05$ **$p < 0.01$ changes from baseline. Figures are mean (SEM) or median (range)

TABLE 58

CHANGES IN SERUM LIPOPROTEINS AT 6 MONTHS AND 1 YEAR ACCORDING TO INITIAL LIPID STATUS

	NORMOLIPIDAEMIC	HYPERCHOLESTEROLAEMIC	HYPERTRIGLYCERIDAEMIC	COMBINED HYPERLIPIDAEMIA
LDL Cholesterol (mmol/l)				
Baseline	3.17 (0.10)	5.55 (0.23)*	3.12 (0.24)	5.31 (0.27)**
6 Months	3.18 (0.11)	4.84 (0.31)	3.36 (0.24)	4.34 (0.49)
1 Year	3.10 (0.12)	4.48 (0.21)	3.32 (0.27)	4.55 (0.43)
HDL Cholesterol (mmol/l)				
Baseline	1.48 (0.04)	1.57 (0.07)	1.27 (0.06)	1.43 (0.09)
6 Months	1.43 (0.04)	1.43 (0.06)	1.21 (0.07)	1.23 (0.08)
1 Year	1.48 (0.03)	1.56 (0.08)	1.27 (0.05)	1.35 (0.03)
Apolipoprotein B (mg/dl)				
Baseline	95 (2)	110 (6)	108 (7)	134 (9)
6 Months	97 (3)	108 (2)	106 (7)	125 (7)
1 Year	97 (2)	117 (5)	98 (7)	132 (9)
HDL_2Cholesterol (mmol/l)				
Baseline	0.77 (0.03)	0.76 (0.09)	0.62 (0.05)	0.64 (0.05)*
6 Months	0.76 (0.04)	0.70 (0.07)	0.57 (0.06)	0.59 (0.09)
1 Year	0.74 (0.03)	0.72 (0.08)	0.65 (0.08)	0.55 (0.07)
HDL_3Cholesterol (mmol/l)				
Baseline	0.71 (0.03)	0.81 (0.06)	0.65 (0.06)	0.78 (0.06)
6 Months	0.66 (0.02)	0.74 (0.05)	0.64 (0.03)	0.64 (0.05)
1 Year	0.74 (0.02)	0.83 (0.05)	0.62 (0.04)	0.80 (0.12)

*$p < 0.05$ **$p < 0.01$ changes from baseline. Figures are mean (SEM)

1:7 DISCUSSION

The series of investigations in this chapter demonstrated that conformational qualitative as well as quantitative abnormalities of lipoproteins are a feature of IDDM. I have been able to demonstrate that lipid metabolism in IDDM is altered not only by prevailing metabolic control, but also by early disturbances of renal function and genetic factors.

In the comparison of diabetic men without renal disease and healthy controls, the most striking features were the marked reductions in levels of apolipoprotein B, of which 90% is contained in low density lipoprotein (LDL). Although the LDL cholesterol level tended if anything to be lower in IDDM,a substantial increase in cholesterol relative to apolipoprotein B was apparent in 'LDL'. The consequent change in density means that the 'LDL' would be more analagous in physical terms to intermediate density lipoprotein (IDL), which may be particularly atherogenic. This particular lipoprotein is characteristically present in large amounts in the serum of patients with type III hyperlipoproteinaemia, which also has clinical features in common with IDDM. A genetic basis for type III hyperlipoproteinaemia is described although co-existant diabetes is often required to allow clinical expression of this disorder (v.i.).

A further finding was the demonstration of higher HDL cholesterol levels in IDDM, which I found was due to an increase in the HDL_3 cholesterol subfraction. Because HDL_3 is normally catabolised to HDL_2 the one logical explanation for the relative excess of HDL_3 and deficiency of HDL_2 would be an increased synthetic and catabolic rate of HDL in IDDM. HDL_3 levels would

then build up but early catabolism would reduce conversion to HDL_2. Glycosylation of HDL may enhance its catabolism (181) which may in part explain the phenomenon.

In my case-control comparison of insulin diabetic patients with normal AER or proteinuria I found evidence that even a minor degree of renal impairment may lead to further alterations in lipid and lipoprotein levels.

Most notably early proteinuria is associated with significant reductions in total HDL and HDL_2 cholesterol levels. This observation raises the possibility that glomeruli in diabetic nephropathy are more porous to HDL_3 and free apolipoprotein AI, thereby compounding the tendency for increased HDL_3 synthesis and consequent urinary loss prior to acquiring sufficient cholesterol to become HDL_2. I also found that HDL cholesterol levels were notably different when isolated by ultracentrifugation or precipitation in patients with nephropathy. Lp(a) has a hydrated density and overlaps with HDL_2. One possible explanation is that therefore Lp(a) is measured as HDL by ultracentrifugation. A higher level of Lp(a) is linked with coronary heart disease and could be compatable with my observations in patients with diabetic nephropathy. Less marked elevations of total and LDL cholesterol, triglycerides and the mass ratio of cholesterol: apo B in LDL were observed. Therefore the lipid profile of patients with nephropathy was more akin to that recognised in general as at high risk for the development of premature atherosclerosis. The novel observation that this group already had an increased prevalence of hypertension and vascular disease may suggest that the

development of quantitative abnormalities of lipids compounding the essential conformational changes in IDDM is implicated in the development of vascular disease. In addition of course, diabetic nephropathy is associated with alterations in platelet function (592), blood viscosity (591, 595) and vascular leakage (590), so it is clear that the abnormalities of lipid metabolism and blood pressure are not acting in isolation to encourage the progression of atherosclerosis and microvascular disease. I would speculate that a 'cascade' of pathological changes acting in synergy is one logical explanation for the association between early nephropathy and vascular disease in IDDM.

In section 1:4 I found that apolipoprotein E polymorphism exerted an effect on lipid and lipoprotein levels in IDDM, just as in the normal population. What was unexpected however, was the marked increase in the prevalence of E2 homozygosity in IDDM. Despite this, only one of the 8 patients who were E2 homozygous had type III hyperlipoproteinaemia, perhaps reflecting in part the fact that the E2 homogygous group had greater C-peptide levels and a lesser duration of diabetes. Residual endogenous insulin secretion may therefore have conferred some protection against the expression of type III hyperlipoproteinaemia.

My conclusion from these studies is that IDDM has several biochemical, genetic and clinical features in common with type III hyperlipoproteinaemia. This is not to say that the conditions are the same, but simply to point out that only a percentage of patients with IDDM develop an excess of vascular disease. The majority of these have diabetic nephropathy which is associated with the abnormalities of lipoproteins. It is

conceivable that associated genetic traits in some cases of diabetic nephropathy modify the metabolism of triglyceride rich lipoproteins such as IDL, where the eventual outcome is similar to that seen in type III hyperlipoproteinaemia. Of course these factors do not operate in isolation to cause hyperlipidaemia in IDDM. Dietary indiscretion is recognised to lead to the hyperlipidaemia in both diabetics and non-diabetics, but was not the subject of intensive scrutiny in my studies.

In the assessment of the prevalence of hyperlipidaemia in IDDM (1:3), I found that hypertriglyceridaemia and combined hyperlipidaemia was commoner in diabetic compared to non-diabetic men, but that hypercholesterolaemia was less common in IDDM without advanced nephropathy. In addition to the previous observations on renal function, hyperlipidaemia in IDDM also appeared to be independently associated with higher daily insulin requirements, obesity, and in the case of hypertriglyceridaemia, with poorer control. This last feature was particularly apparent in the longitudinal studies, when hypertriglyceridaemia was found to be the most amenable to correction following improved glycaemic control. On the other hand those patients with combined hyperlipidaemia tended to remain hyperlipidaemic. The higher daily insulin dose and poorer glycaemic control in the patients with combined hyperlipidaemia may be related, and suggest that insulin resistance may be the common link in this group.

Despite the suggestion that combined hyperlipidaemia is relatively more resistant to correction, the short term and long

term longitudinal studies revealed that considerable changes in lipid metabolism accompany improved glycaemic control and diabetic management. I found that the prevalence of hyperlipidaemia halved during the initial 6 week period of intensified management, predominantly due to a reduction in hypertriglyceridaemia, although the number of subjects with hypercholesterolaemia also halved.

Levels of apoliprotein B were essentially unaltered during this period with the exception of the combined hyperlipidaemic group, where a marked reduction was noted. As most of the fall in cholesterol took place within the LDL fraction, it would appear that intensive therapy is capable of altering the conformational changes in LDL to some extent, particularly in patients with hypercholesterolaemia.

Although HDL cholesterol levels did not fall during the first 6 weeks in the total group (Table 30), a substantial fall was recorded in those patients with combined hyperlipidaemia, in whom levels of both HDL_2 and HDL_3 cholesterol fell. I found that HDL_3 cholesterol levels fell significantly in all the sub-groups over this period, which may reflect a general decrease in synthesis. HDL_2 levels otherwise remained unaltered (or increased in those with hypercholesterolaemia) so it would appear that intensified therapy does not lead to any undesirable changes in the cardioprotective component of HDL.

Although metabolic control was less tight following the 6 week period intensive management, lipid levels tended to run slightly lower in the study group than the controls, so it would appear that improvements in lipid metabolism were maintained for

at least 1 year, at least in some cases. This appears to have been due mainly to sustained reductions in LDL cholesterol and triglycerides, since HDL cholesterol levels remained fairly constant, with the exception of the combined hyperlipidaemic group where HDL_2 cholesterol levels showed a continued fall over the year.

In addition to demonstrating that lipid levels may been lowered in patients who were initially hyperlipidaemic, I found that 10 patients who were originally normolipidaemic became hyperlipidaemic. It appears therefore that the development of hyperlipidaemia in IDDM is not 'preconditioned', and may arise for a multitude of reasons. Improved diabetic management can make a considerable sustained impact on hyperlipidaemia, although it is perhaps less effective in cases of combined hyperlipidaemia associated with early diabetic nephropathy and/or insulin resistance.

CHAPTER 5

ASSESSMENTS OF CLINICAL VALUE OF FRUCTOSAMINE AND GLYCOSYLATED SERUM ALBUMIN IN THE MEASUREMENT OF GLYCAEMIC CONTROL IN IDDM

1:1 CROSS-SECTIONAL STUDY OF DIRECT MEASURES OF GLYCAEMIA AND GLYCOSYLATED BLOOD PROTEINS IN NORMOLIPIDAEMIC AND HYPERLIPIDAEMIC IDDM.

I examined associations between direct measures of glycaemia and the various glycosylated blood proteins basally in 113 subjects (68 males, 45 females) in whom data was complete, and examined whether or not the 'fructosamine' assay was affected by varying serum concentrations of lipids, albumin or C-peptide. The patients were aged 40.3 (1.1) years (mean (SEM)), (range 15-69 years), and had been diabetic for 13.1 (0.8) years (range 4 months - 57 years). They were of average body mass index (BMI 23.6 (0.8), range 15-35), and had preserved renal function (urea 5.3 (0.1) mmol/l) and normoalbuminaemia (range 37-51g/l). 54 (49%) of the subjects had no detectable C-peptide response following a standard meal. The glycaemic variables were measured on admission to the home blood glucose monitoring study during the initial 24 hour stay in hospital. The M value of Schlichtkrull (97) was calculated, using an arbitrary normal blood glucose level of 4.4mmol/l, by the equation:

$$\text{M-value} = \left(\frac{10 \log_{10} x}{4.4}\right)^{3} / n + y$$

where x is the blood glucose value, y the difference between the maximum and minimum value and n the number of blood glucose measurements made (in this case 10). Fructosamine levels were assessed directly and after correction to a standard albumin concentration of 40g/l.

Results Fructosamine levels were 3.92 (0.08) mmol/l, corrected to 3.57 (0.08) mmol/l after standardisation to an albumin concentration of 40g/l, glycosylated serum albumin (GSA) 9.8 (0.4) %, HbA_1 9.1 (0.2) %, serum albumin 44.2 (0.3) g/l, cholesterol 5.69 (0.14) mmol/l and triglycerides 1.80 (0.22) mmol/l (range 0.39-23.29mmol/l). Neither fructosamine or GSA values were significantly altered by correction for prevailing albumin concentrations. Fasting blood glucose levels were 11.1 (0.6) mmol/l, mean blood glucose 12.5 (0.3) mmol/l and the M value 117 (7) units.

29 (26%) had fasting hypercholesterolaemia (greater than 6.5mmol/l) and 24 (21%) were hypertriglyceridaemic (greater than 2.25 mmol/l). C-peptide levels ranged from 0-2.5pmol/ml (median 0.027 pmol/ml).

Serum fructosamine levels correlated closely with corrected fructosamine levels ($r=0.95$, $p=0.001$), but less so with GSA ($r=0.48$, $p=0.001$) (Figure 24), HbA_1 ($r=0.44$; $p=0.001$) (Figure 25) or levels of fasting blood glucose ($r=0.35$, $p=0.001$), mean blood glucose ($r=0.30$, $p=0.001$) and the M value ($r=0.33$, $p=0.001$) (Table 58a). Fructosamine levels did not correlate with serum levels of albumin, cholesterol or triglycerides. After fructosamine was corrected to a standard albumin concentration of 40g/l,correlations were essentially the same, except that the corrected levels inversely correlated with serum albumin ($r=-0.32$, $p=0.001$).

GSA correlated more closely with HbA_1 ($r=0.68$, $p<0.001$) (Figure 26), the M value ($r=0.42$, $p=0.001$), and fasting ($r=0.37$,$p=0.001$) and mean blood glucose levels ($r=0.39$, $p=0.001$)

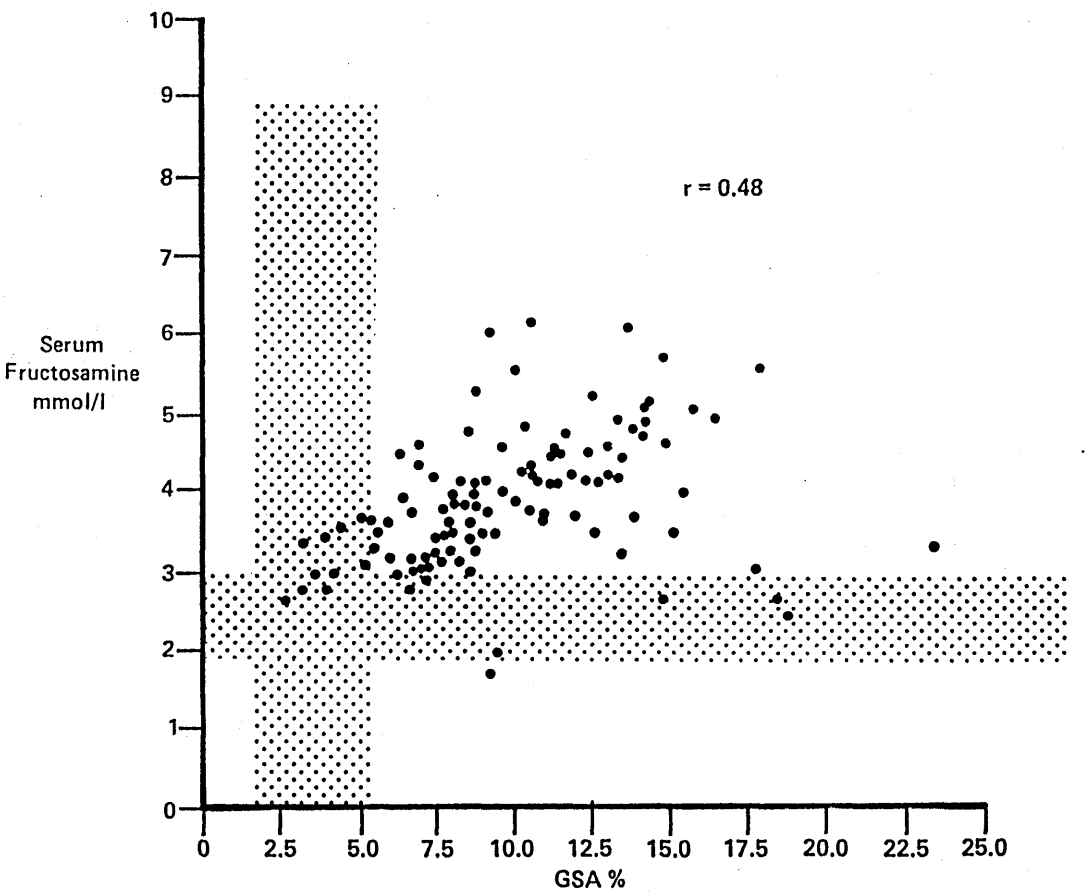


FIG. 24 Correlation between GSA and fructosamine values in 113 subjects with IDDM.

Shaded area represents normal ranges

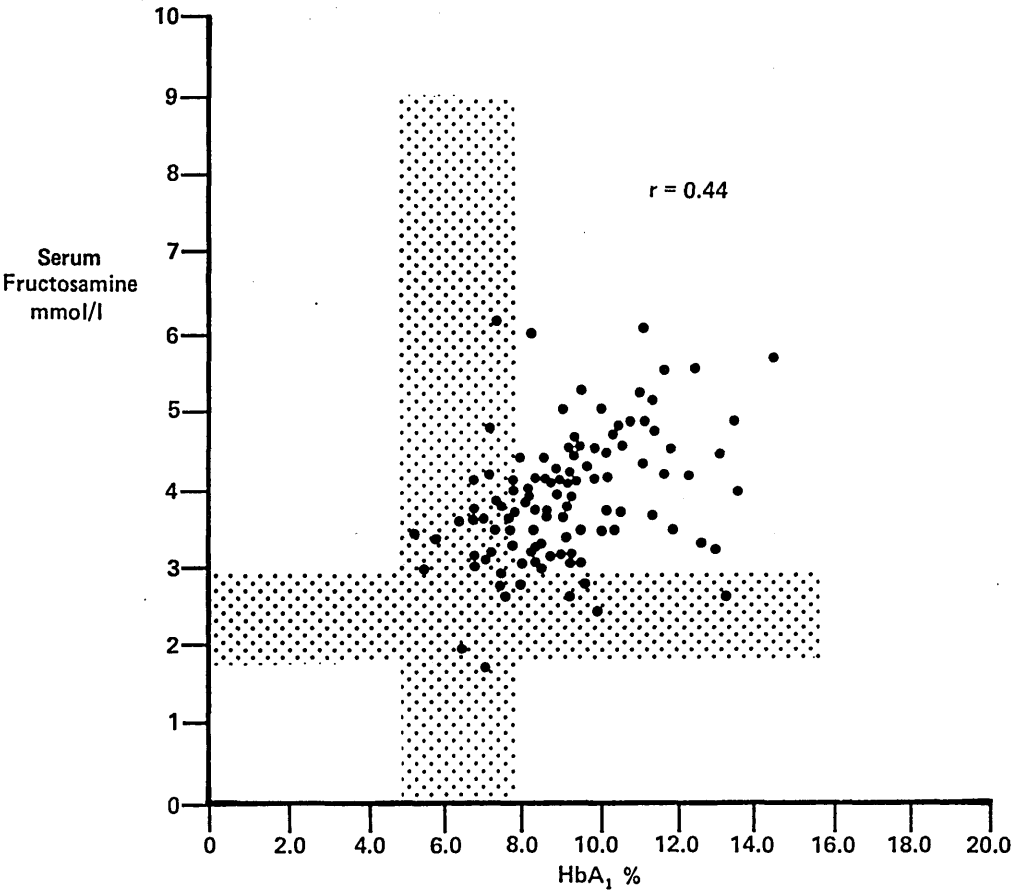


FIG. 25 Correlation between HbA_1 and fructosamine values in 113 subjects with IDDM.

Shaded area represents normal ranges

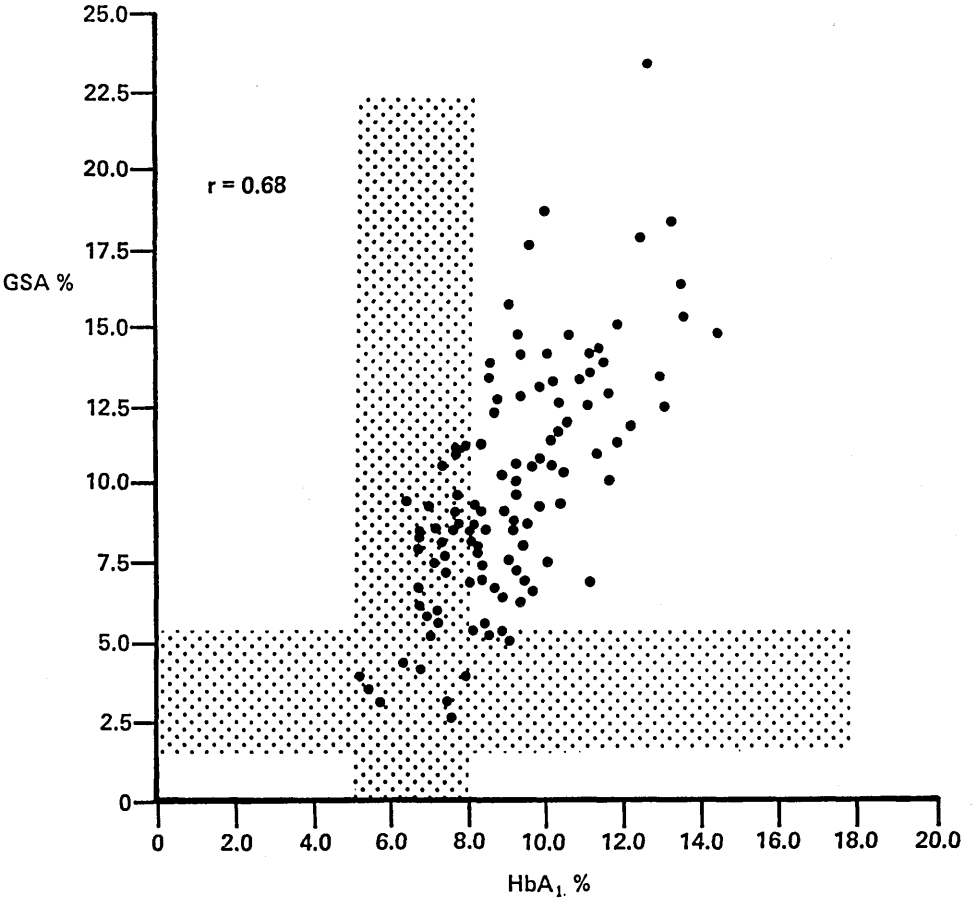


FIG. 26 Correlation between GSA and HbA_1 values in 113 subjects with IDDM.

Shaded area represents normal ranges

TABLE 58a

Correlation between direct measures of glycaemia and glycosylated blood proteins in 113 subjects with insulin dependent diabetes mellitus (IDDM)

	HbA_1	Fructosamine	GSA
Fasting Blood Glucose	r = 0.34	r = 0.35 (r = 0.37)*	r = 0.37
Mean Blood Glucose	r = 0.35	r = 0.30 (r = 0.31)*	r = 0.39
M Value	r = 0.35	r = 0.33 (r = 0.34)*	r = 0.42

*Fructosamine values corrected to serum albumin concentration of 40g/l.

p for all correlations = 0.001

TABLE 58b

MEASURES OF GLYCAEMIC CONTROL IN 29 HYPERCHOLESTEROLAEMIC AND 84 NORMOCHOLESTEROLAEMIC IDDM SUBJECTS Figures are mean (SEM)

	Hypercholesterolaemic IDDM	Normocholesterolaemic IDDM
HBA_1 (%)	9.3 (0.4)	9.0 (0.2)
Fasting blood Glucose (mmol/l)	12.5 (1.1)	10.6 (0.2)
Mean blood Glucose (mmol/l)	12.6 (0.6)	12.5 (0.4)
M Value (units)	116 (12)	119 (9)
GSA (%)	10.0 (0.7)	9.7 (0.4)
Fructosamine (mmol/l)	3.87 (0.17)	3.93 (0.09)
Serum Albumin (g/l)	43.4 (0.6)	44.5 (0.3)
Collected Fructosamine (mol/l)	3.59 (0.18)	3.56 (0.09)

Figures are mean (SEM).

in comparison to fructosamine (Table 58a). There was no correlation between GSA and cholesterol (r=0.03) or with serum albumin (r=-0.01) but a weak relationship with triglyceride levels (r=0.26, p=0.003) was recorded.

When the 29 hypercholesterolaemic subjects were compared to those 84 with normocholesterolaemia, no difference was recorded for any measure of glycaemic control including fructosamine levels (3.87 (0.17) V 3.93 (0.09) mmol/l, respectively). (Table 58b). However, whilst levels of fasting blood glucose and GSA were significantly greater ($p<0.03$) in the 24 hypertriglyceridaemic patients than in those with normotriglyceridaemia, levels of fructosamine tended to be lower (Table 58c). Furthermore, after correction for the difference in fasting blood glucose, fructosamine levels were significantly reduced ($p<0.05$) in patients with hypertriglyeridaemia (Table 58c). No such effect was observed for GSA levels.

C-peptide levels correlated inversely with fasting blood glucose (r=-0.30, p=0.001), fructosamine (r= -0.26, p=0.008) and corrected fructosamine (r=-0.24, p=0.002), and to a lesser extent with the M values (r= -0.25,p=0.005), GSA (r= -0.22, p=0.01), the mean blood glucose value (r= -0.18, p n/s) and HbA_1 (r= -0.16, p n/s). In the 59 patients with detectable C-peptide, closer inverse correlations were recorded with mean blood glucose levels (r= -0.32, p=0.007), M values (r= -0.36, p=0.003), and the HbA_1 (r= -0.24,p=0.03) than when all patients were included in the analysis, although this was not the case for either GSA (r= -0.15, pn/s) or fructosamine (r=0.05, pn/s).

TABLE 58c

Measures of glycaemic control in 24 hypertriglyceridaemic and 89 normotriglyceridaemic patients with IDDM

	Hypertriglyceridaemic IDDM	Normotriglyceridaemic IDDM
Triglyerides (mmol/l)	3.04 (2.29-23.29)	1.05 (0.39-2.24)
Fasting Blood Gluose (mmol/l)	13.6 (1.3)	10.4 (0.6)*
Mean Blood Glucose (mmol/l)	13.8 (0.8)	12.1 (0.4)
M Value (units)	144 (18)	111 (7)
HbA_1 (%)	9.9 (0.5)	8.9 (0.2)
GSA (%)	11.8 (0.9)	9.3 (0.4)*
Fructosamine (mmol/l)	3.79 (0.16)+	3.95 (0.09)
Serum Albumin (g/l)	44.2 (0.3)	43.9 (0.4)
Corrected Fructosamine (mmol/l)	3.50 (0.16)	3.59 (0.09)

Figures are median (range) or mean (SEM)

*p <0.03

+p< 0.05 significantly lower than normotriglyceridaemic group after correction for fasting blood glucose levels.

1:2 PROSPECTIVE EVALUATION OF THE RELATIVE CLINICAL UTILITY OF GSA AND FRUCTOSAMINE DURING SHORT TERM IMPROVEMENTS IN GLYCAEMIC CONTROL

I assessed changes in GSA, fructosamine, HbA_1 and direct measures of glycaemia during the initial 6 week period when attempts were made to improve glycaemic control. Of the 113 subjects who were analysed initially, comprehensive data was available in 100 cases. Direct measures of glycaemia were based on patient-generated data verified by measuring stored blood sticks in a hospital blood glucose reflectance meter and by validation with filter card blood glucose measurements.

Cross sectional analysis of the data collected after 2, 4 and 6 weeks was carried out, and in addition levels of GSA, fructosamine and HbA_1 were compared with the direct measures of glycaemia made 2, 4 and 6 weeks previously. Finally, a comparison was made of the relative ability of GSA, HbA_1 and fructosamine to reflect improvements in glycaemia over periods of 2 weeks (Δ 2 weeks, 4 weeks (Δ 4 weeks) and 6 weeks (Δ 6 weeks).

RESULTS

1. Patterns of Glycaemia During 6 weeks improved glycaemic control (Figures 27 and 28).

Marked improvements were recorded in all direct measures of glycaemia after the initial 2 week period ($p=0.001$) Figure 27). These were paralleled by significant reductions in GSA, fructosamine ($p=0.001$), and corrected fructosamine ($p<0.01$) to a lesser degree (v.i.) (Figure 28). By 4 and 6 weeks, further falls in all measures of glycaemic control had taken place in

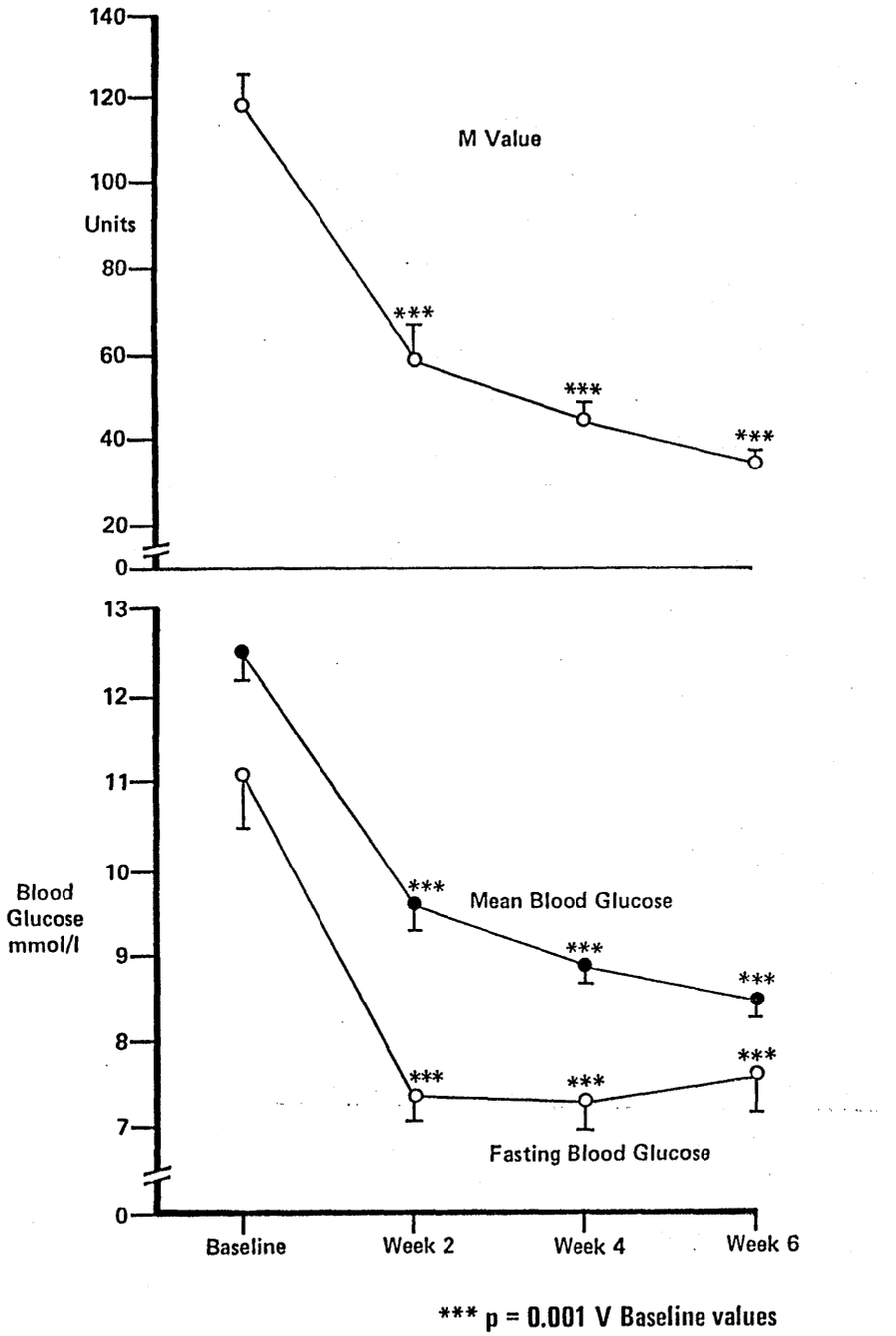


FIG. 27 Serial changes over 6 weeks in direct measures of glycaemia in 100 subjects with IDDM.

Figures represent Mean ± SEM

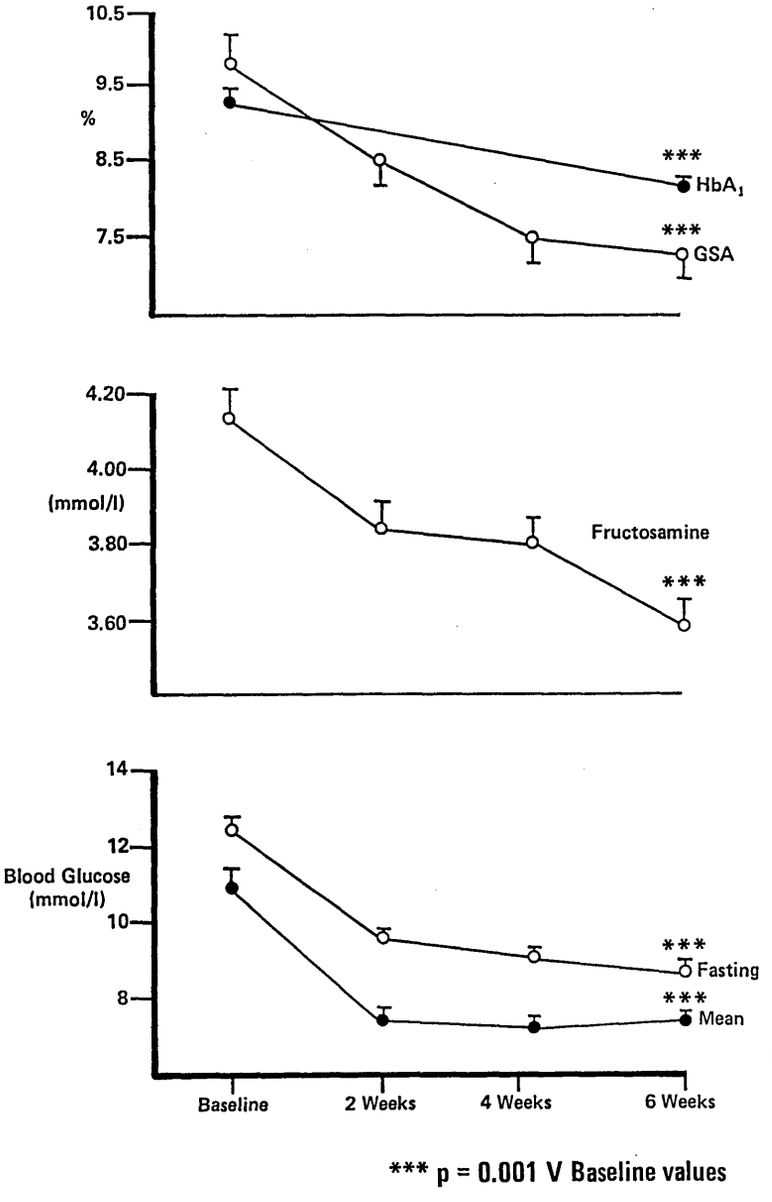


FIG. 28 Serial changes over 6 weeks in serum albumin and glycosylated blood proteins in 100 subjects with IDDM.

Figures represent Mean ± SEM

comparison to initial values ($p<0.001$) (Figures 27 and 28).

2. Cross Sectional Correlations between direct measures of glyaemia and glycated blood proteins (Table 59)

Fasting blood glucose correlated to a greater or lesser extent at the initial, 2, 4 and 6 week time points with levels of GSA (r_s range 0.22 to 0.44) and with fructosamine levels (r_s range 0.21 to 0.39) although corrected fructosamine levels were not always correlated. Mean blood glucose levels were more closely related at the same time points to levels of GSA (r_s range 0.30 to 0.50) and both corrected and direct fructosamine levels (r_s range 0.30 to 0.50). Likewise M values reflected measures of GSA (r_s range 0.31 to 0.52) and of direct and corrected fructosamine (r_s range 0.33 to 0.49).

GSA levels correlated with fructosamine (corrected and direct) at all time points (r_s range 0.46 to 0.66), but there was no suggestion that the measurements closely paralleled one another.

HbA_1 was more highly correlated with GSA than fructosamine both initially (r_s=0.68 Vs 0.42 to 0.44) and after 6 weeks (r_s=0.47 Vs 0.22 to 0.23).

3. Cross sectional comparisons of direct measure of glycaemia and subsequent GSA and fructosamine levels (Table 60)

Poor correlation was observed when initial fasting blood glucose levels were compared with GSA and fructosamine values at 2 and 6 weeks. 2 and 4 weeks fasting blood glucose concentrations showed improved correlations with 4 and 6 week GSA levels and with fructosamine levels at 6 weeks.

TABLE 59

CROSS SECTIONAL CORRELATIONS BETWEEN DIRECT MEASURES OF GLYCAEMIA, HbA_1, GSA AND FRUCTOSAMINE IN 100 SUBJECTS WITH IDDM AT DIFFERENT TIME POINTS

	GSA				FRUCTOSAMINE			
	Initial	2 weeks	4 weeks	6 weeks	Initial	2 weeks	4 weeks	6 weeks
Fasting Blood Glucose	0.37*	0.22***	0.30**	0.44***	0.35*** (0.37)***	0.22* (0.15)	0.22* (0.15)	0.39*** (0.36)***
Mean Blood Glucose	0.39***	0.30**	0.47***	0.50***	0.30*** (0.31)***	0.39*** (0.41)***	0.48*** (0.47)***	0.50*** (0.48)***
M Value	0.42***	0.31***	0.46***	0.52***	0.33*** (0.34)***	0.41*** (0.43)***	0.45*** (0.44)***	0.49*** (0.48)***
Fructosamine	0.48*** (0.46)***	0.66*** (0.63)***	0.54*** (0.46)***	0.52*** (0.48)***	---	---	---	---
GSA	---	---	---	---	---	---	---	---
HbA_1	0.68***	---	---	0.47***	0.44*** (0.42)***	---	---	0.22** (0.23)**

Figures are correlation coefficients (r_s). Figures in brackets refer to corrected fructosamine data.
*p < 0.05 **p < 0.01 ***p ≤ 0.001

TABLE 60

COMPARISONS OF DIRECT MEASURES OF GLYCAEMIA WITH SUBSEQUENT GSA AND FRUCTOSAMINE LEVELS IN 100 SUBJECTS WITH IDDM

	GSA			FRUCTOSAMINE		
	2 weeks	4 weeks	6 weeks	2 weeks	4 weeks	6 weeks
Fasting Blood Glucose Levels						
Initial (Basal)	0.17	0.25**	0.20*	0.25** (0.20)*	0.31** (0.28)**	0.12 (0.11)
Week 2	---	0.33***	0.38***	---	0.15 (0.11)	0.18 (0.18)
Week 4	---	---	0.40***	---	---	0.36*** (0.27)**
Mean Blood Glucose Levels						
Initial (Basal)	0.30**	0.28**	0.20*	0.31*** (0.29)**	0.26** (0.24)**	0.12 (0.12)
Week 2		0.42***	0.32***	---	0.37*** (0.36)***	0.30** (0.32)***
Week 4	---	---	0.39***	---	---	0.34*** (0.34)***
M Value						
Initial (Basal)	0.33***	0.33***	0.23**	0.33*** (0.31)***	0.27** (0.24)**	0.12 (0.12)
Week 2	---	0.44***	0.32***	---	0.36*** (0.35)***	0.32*** (0.34)***
Week 4	---	---	0.36***	---	---	0.35*** (0.35)***

Figures are correlation coefficients (r_s)
Figures in brackets refer to corrected fructosamine data
*p < 0.05 **p < 0.01 ***p < 0.001

On the other hand mean blood glucose levels initially and at 2 and 4 weeks were correlated significantly with subsequent measures of GSA at all time points and to a lesser extent with fructosamine at most time points. A similar observation was made with M values and subsequent GSA or fructosamine levels.

Overall, direct measures of glycaemia were more highly correlated with GSA than with fructosamine.

4. Comparison of changes ($\triangle$) in direct measures of glycaemia and glycated blood proteins (Tables 61 - 63)

The extent of the falls in all glycaemic measures from baseline are shown in Table 61. Direct glycaemic measures fell after 6 weeks by 30-56% from their original levels, whilst GSA fell by 26% and fructosamine and HbA_1 only fell by 11-13%.

$\triangle$ HbA_1, $\triangle$ fructosamine and $\triangle$ GSA significantly reflected the $\triangle$ fasting, $\triangle$ mean blood glucose and the $\triangle$ M value over 6 weeks. However over 2 and 4 weeks $\triangle$ GSA was more closely related to changes in direct measures of glycaemia than $\triangle$ fructosamine (Table 62).

Furthermore, although $\triangle$ HbA_1 and $\triangle$ fructosamine over 6 weeks correlated with one another, changes in GSA and fructosamine over 2-6 weeks did not parallel one another (range 0.51 to 0.57) (Table 63).

1:3. A COMPARISON OF LONG TERM CHANGES IN GSA, FRUCTOSAMINE AND OTHER MEASURES OF GLYCAEMIC CONTROL OVER A PERIOD OF 1 YEAR

I was able to analyse and compare the different measures of glycaemia in 98 subjects during the 1st year of the home blood

TABLE 61

EXTENT OF CHANGES IN MEASURES OF GLYCAEMIA DURING 6 WEEKS OF IMPROVED CONTROL IN 100 SUBJECTS WITH IDDM

TIME	ΔFASTING BLOOD GLUCOSE (mmol/l)	ΔMEAN BLOOD GLUCOSE (mmol/l)	ΔM VALUE (UNITS)	ΔGSA (%)	ΔFRUCTOSAMINE (mmol/l)	ΔCORRECTED FRUCTOSAMINE (mmol/l)	ΔHbA_1 (%)
2 WEEKS	3.9 (0.6) (35%)	2.9 (0.4) (23%)	58 (8) (49%)	1.5 (0.2) (15%)	0.23 (0.08) (6%)	0.19 (0.07) (5%)	-----
4 WEEKS	3.8 (0.6) (34%)	3.6 (0.3) (29%)	73 (7) (62%)	2.2 (0.4) (22%)	0.35 (0.11) (9%)	0.30 (0.10) (8%)	-----
6 WEEKS	3.6 (0.5) (32%)	3.7 (0.3) (30%)	78 (7) (66%)	2.5 (0.3) (26%)	0.50 (0.10) (13%)	0.41 (0.10) (11%)	1.1 (0.1) (12%)

Figures are absolute fall expressed as mean (SEM) and as % fall from initial value

TABLE 62

COMPARISON OF CHANGES (Δ) IN DIRECT MEASURES OF GLYCAEMIA AND GLYCATED BLOOD PROTEINS OVER 2, 4 and 6 WEEK PERIODS IN 100 SUBJECTS WITH IDDM

	ΔFASTING BLOOD GLUCOSE	Δ MEAN BLOOD GLUCOSE	ΔM VALUE
ΔHbA_1			
. over 6 weeks	0.16*	0.22**	0.24**
ΔGSA			
. over 2 weeks	0.37***	0.28**	0.26**
. over 4 weeks	0.28**	0.36***	0.32***
. over 6 weeks	0.38***	0.36***	0.38***
ΔFRUCTOSAMINE			
. over 2 weeks	0.18*	0.00	0.01
. over 4 weeks	0.13	0.19*	0.20*
. over 6 weeks	0.18*	0.16*	0.18*
ΔCORRECTED FRUCTOSAMINE			
. over 2 weeks	0.28**	0.00	0.01
. over 4 weeks	0.20*	0.19*	0.20*
. over 6 weeks	0.20*	0.17*	0.23**

Figures are correlation coefficients (r_s)

*$p < 0.05$ **$p \leqslant 0.01$ ***$p < 0.001$

TABLE 63

COMPARISON OF CHANGES (Δ) IN GLYCATED BLOOD PROTEINS OVER 2, 4 and 6 WEEK PERIODS OF IMPROVED CONTROL IN 100 SUBJECTS WITH IDDM

	GSA	FRUCTOSAMINE	CORRECTED FRUCTOSAMINE	HbA_1
ΔHbA_1				
. over 6 weeks	0.52***	0.42***	0.43***	----
ΔGSA				
. over 2 weeks	----	0.56***	0.57***	----
. over 4 weeks	----	0.53***	0.54***	----
. over 6 weeks	----	0.27**	0.25	0.52***
ΔFRUCTOSAMINE				
. over 2 weeks	0.56***	----	0.89***	----
. over 4 weeks	0.53***	----	0.91***	----
. over 6 weeks	0.27**	----	0.92***	0.42***
ΔCORRECTED FRUCTOSAMINE				
. over 2 weeks	0.57***	0.89***	----	----
. over 4 weeks	0.54***	0.91***	----	----
. over 6 weeks	0.25**	0.92***	----	0.43***

Figures are correlation coefficients (r_s)

**p < 0.01 ***p < 0.001

glucose monitoring study.

Firstly I examined potential associations between the various measures of control throughout the year. Glycated blood proteins were compared with various direct measures of glycaemia calculated from filter cards returned over the preceeding 3 month interval.

I also carried out Kappa Cohen analysis on the various measures of glycaemia at 3 monthly intervals to assess how frequently absolute discordance or concordance was observed between the various measures of glycaemic control. For this exercise I graded glycaemic control as excellent, fair or poor for each of the variables. Classification categories for the various measures are shown in Table 64.

Finally I compared other measures of control in a subgroup of subjects whose HbA_1 levels were persistently less than or equal to 8.0% following the 6 week period of intensified management, at each 3 month interval during the first year of the study.

TABLE 64

Glycaemic Control Categories

	Excellent	Fair	Poor
HbA_1 (%)	< 8.0	8.0-10.0	> 10.0
GSA (%)	< 6.0	5.0-8.0	> 8.0
Fructosamine (mmol/l)	< 3.00	3.00-3.50	> 3.50
Filter Card Mean Fasting Blood Glucose (mmol/l)	< 7.0	7.0-10.0	> 10.0
Filter Card Blood Glucose M Value (Units)	< 15	15-50	> 50

RESULTS

The number of completed filter cards returned that were suitable for analysis in the 98 subjects was variable and ranged from 67-98 (mean 80) per month.

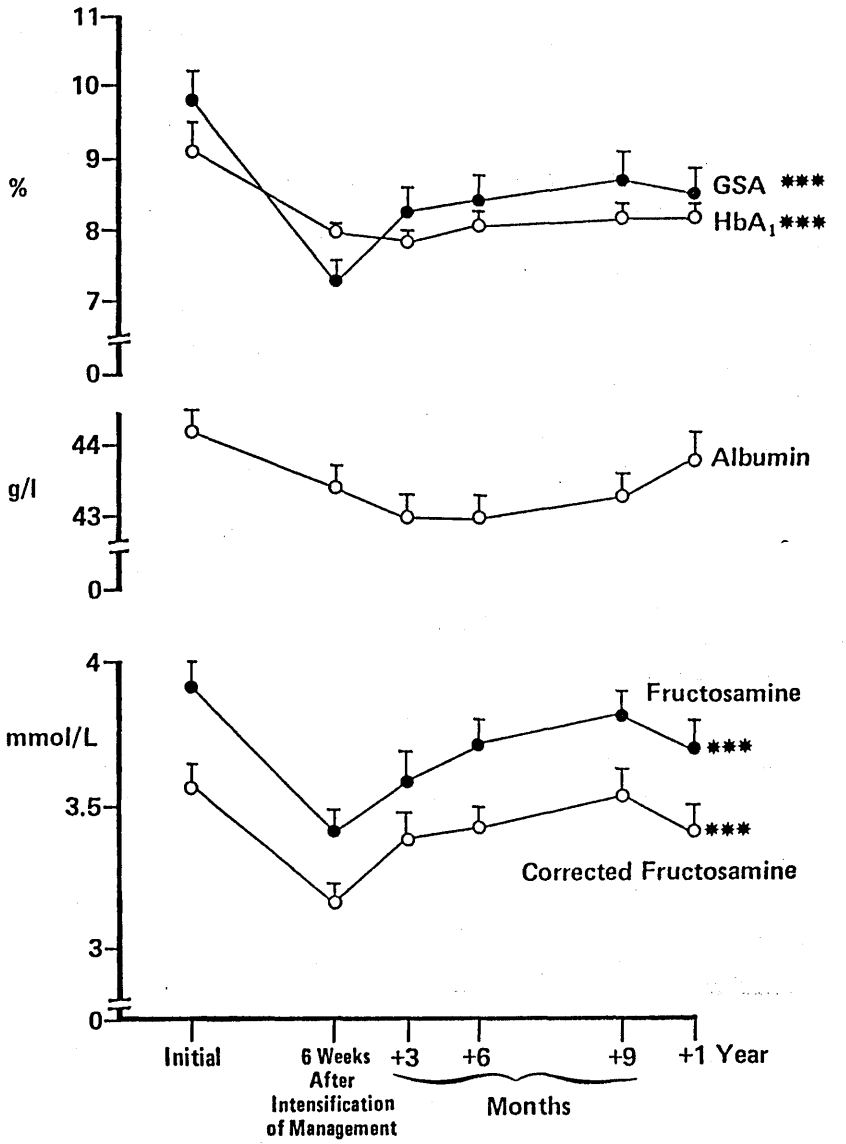
1. Serial changes in glycaemic measures over course of the study (Figures 29-31)

Significant changes were observed in all measures of glycaemic control, mainly due to the improvement in glycaemic control during the 6 week period of intensified management. However in addition GSA and direct and correct fructosamine levels rose significantly thereafter, despite little further change in HbA_1 or direct measures of glycaemia. Serum albumin levels remained stable throughout the study.

2. Correlations between different measures of glycaemic control over 1 year (Figures 32-35)

Because of the many comparisons, only $p<0.001$ is considered significant. Considerable variation was recorded in the correlation between fasting blood glucose and glycosylated blood protein levels. Fructosamine showed a significant correlation on only 3 of 14 occasions (r_s range 0.35 to 0.39), GSA on only 2 out of the 14 occasions (r_s range 0.37 to 0.44) as did HbA_1 (r_s range 0.34 to 0.37) (Figure 32).

On the other hand, the relationship between mean blood glucose and glycosylated blood protein levels was more clearly defined (Fig. 33). Whilst fructosamine only correlated significantly on 4 of 14 occasions (r_s 0.30 to 0.50), GSA was related on 6 occasions (r_s range 0.36 to 0.54) as was HbA_1 (r_s range 0.36 to 0.48). Likewise M values were significantly



*** $p < 0.001$ Significance of change through the year

FIG. 29 *Changes in glycosylated blood proteins and serum albumin over 1 year.*

Figures represent Mean ± SEM

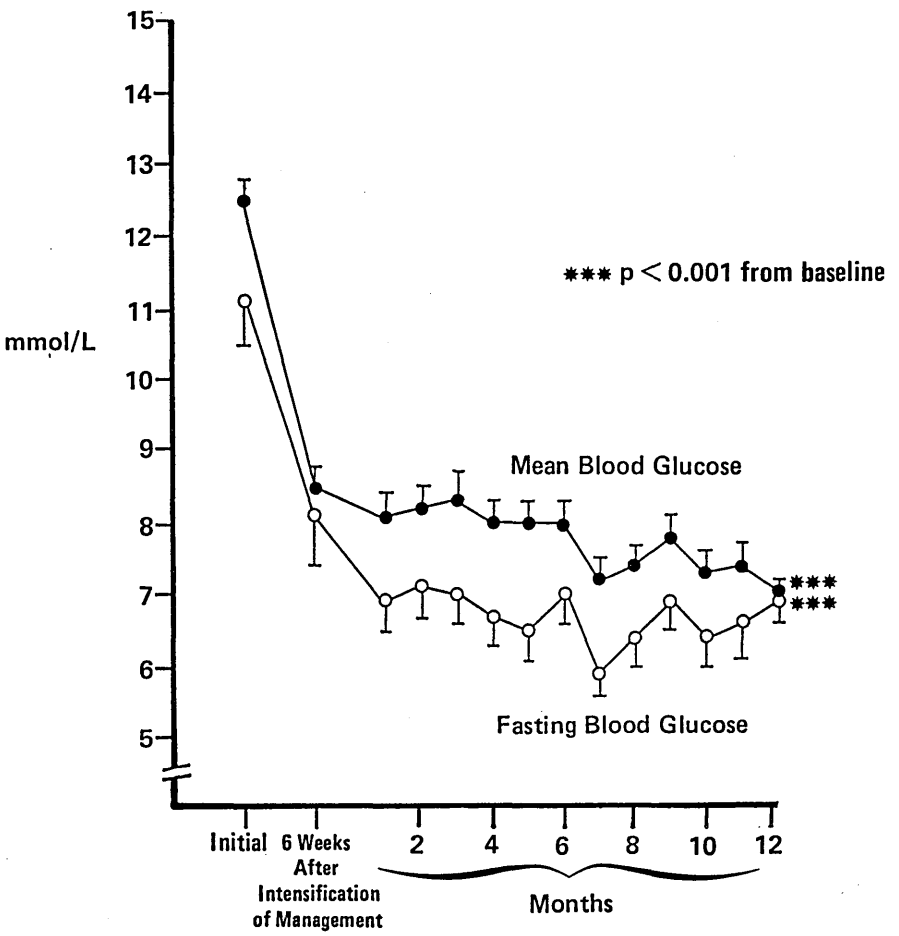


FIG. 30 Changes in fasting and mean blood glucose values over 1 year.

Figures represent Mean ± SEM

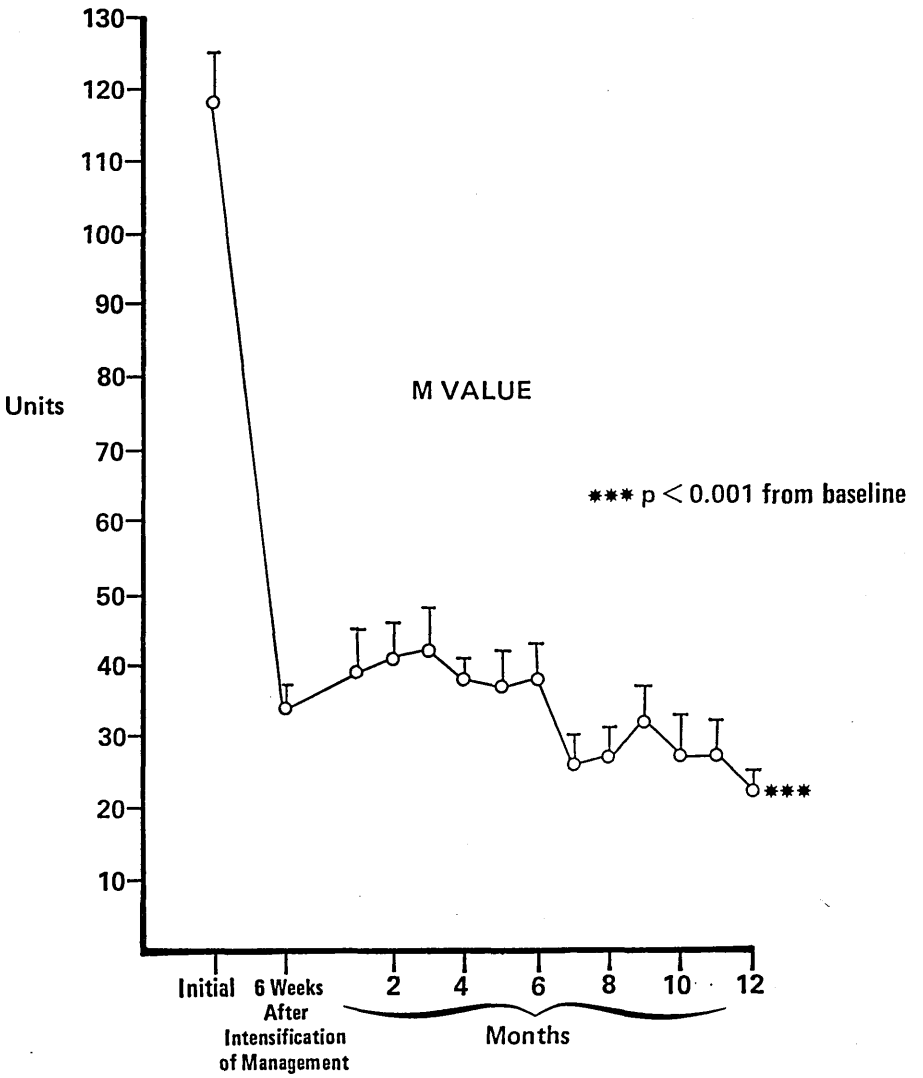


FIG. 31 Changes in the M value over 1 year.

Figures represent Mean ± SEM

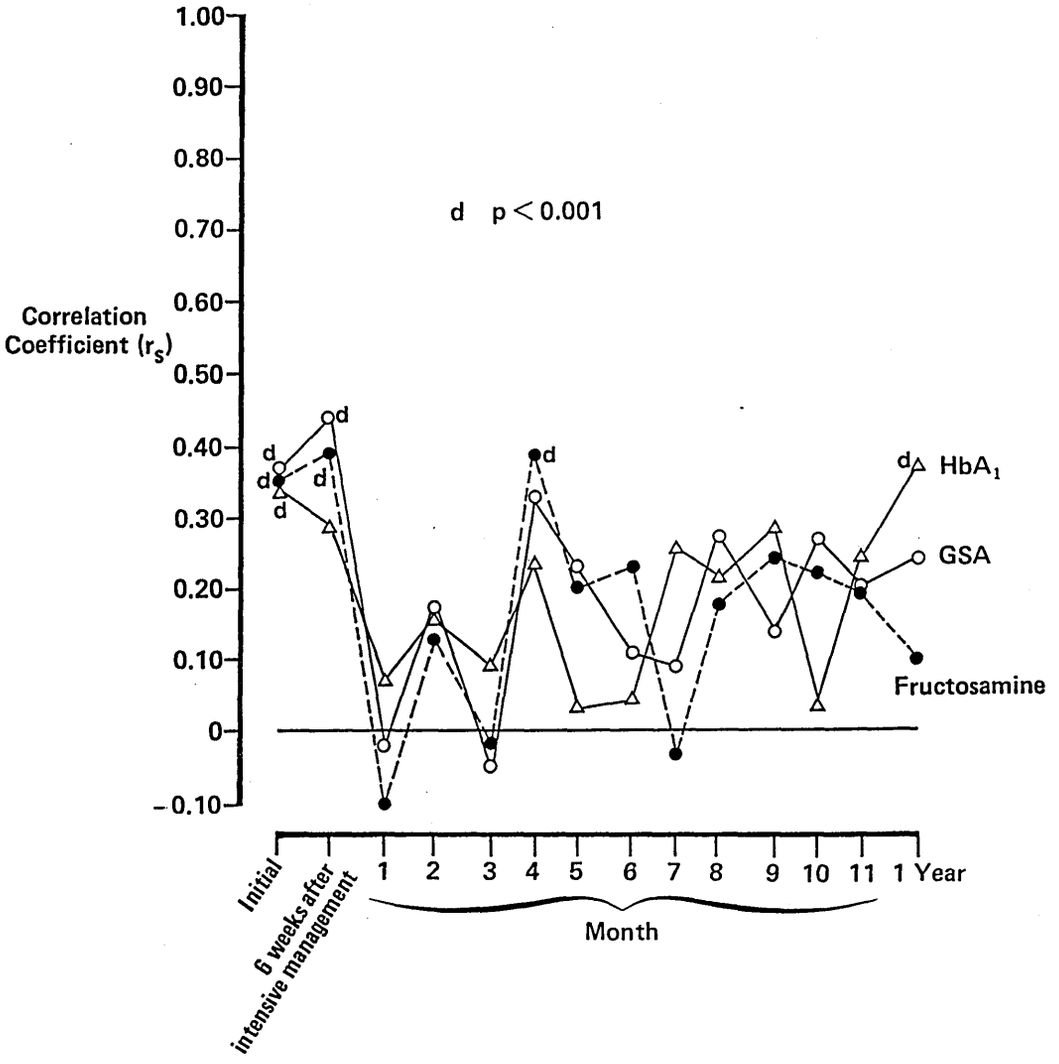


FIG. 32 Correlations between fasting blood glucose and glycosylated blood proteins over the course of 1 year.

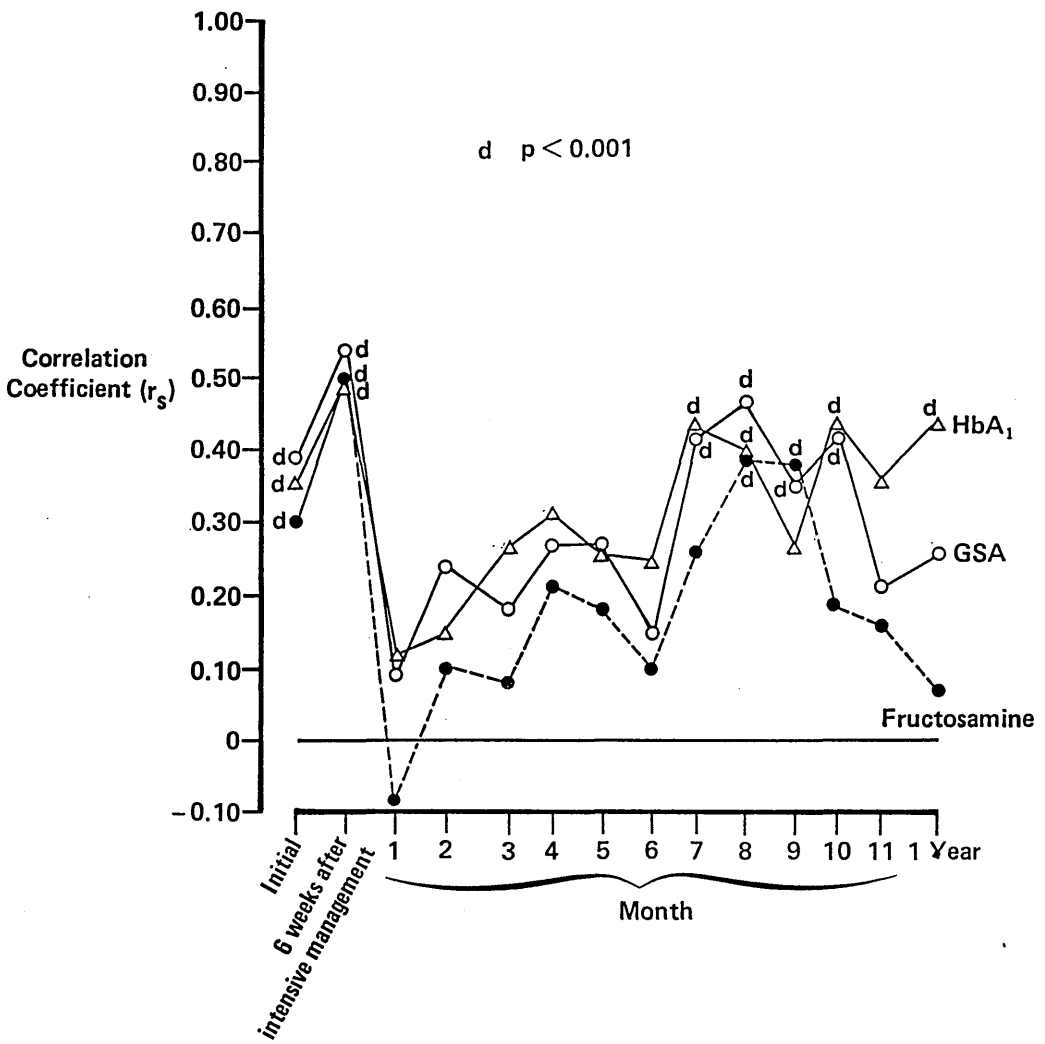


FIG. 33 Correlations between mean blood glucose and glycosylated blood proteins over the course of 1 year.

related to HbA_1 on 7 occasions (r_s range 0.34 to 0.45), but only to fructosamine on 4 occasions (r_s range 0.32 to 0.50) and GSA on 4 (r_s range 0.42 to 0.58) (Fig. 34).

Correlations between various glycated blood proteins confirmed a continued significant association throughout the year between HbA_1 and GSA (r_s range 0.47 to 0.68), and between GSA and fructosamine (r_s range 0.48 to 0.76). The correlations between HbA_1 and fructosamine were less clear (r_s range 0.38 to 0.44) and no significant correlation was apparent at the point of randomisation or at 3 months (Fig. 35).

3.Comparison of different measures of glyaemic control categories (Tables 65 and 66)

The extent of agreement between the various glycaemic measures was studied throughout the year using the control categories from Table 64 to represent excellent, fair or poor control. Absolute concordance was present when both variables simultaneously were categorised in the same control group whilst absolute discordance referred to when 1 measure was categorised as 'excellent' whilst the other was recorded as 'poor'.

Comparison of HbA_1 and fructosamine levels showed that absolute discordant values were recorded on between 16-29% of values during the year, and no significant agreement was recorded between these variables during the year. On the other hand a closer degree of association was observed between GSA and HbA_1, where discordant data was recorded on between 11-19% of the values during the year, but where significant associations were recorded at baseline, the point of randomisation, 9 months and 1

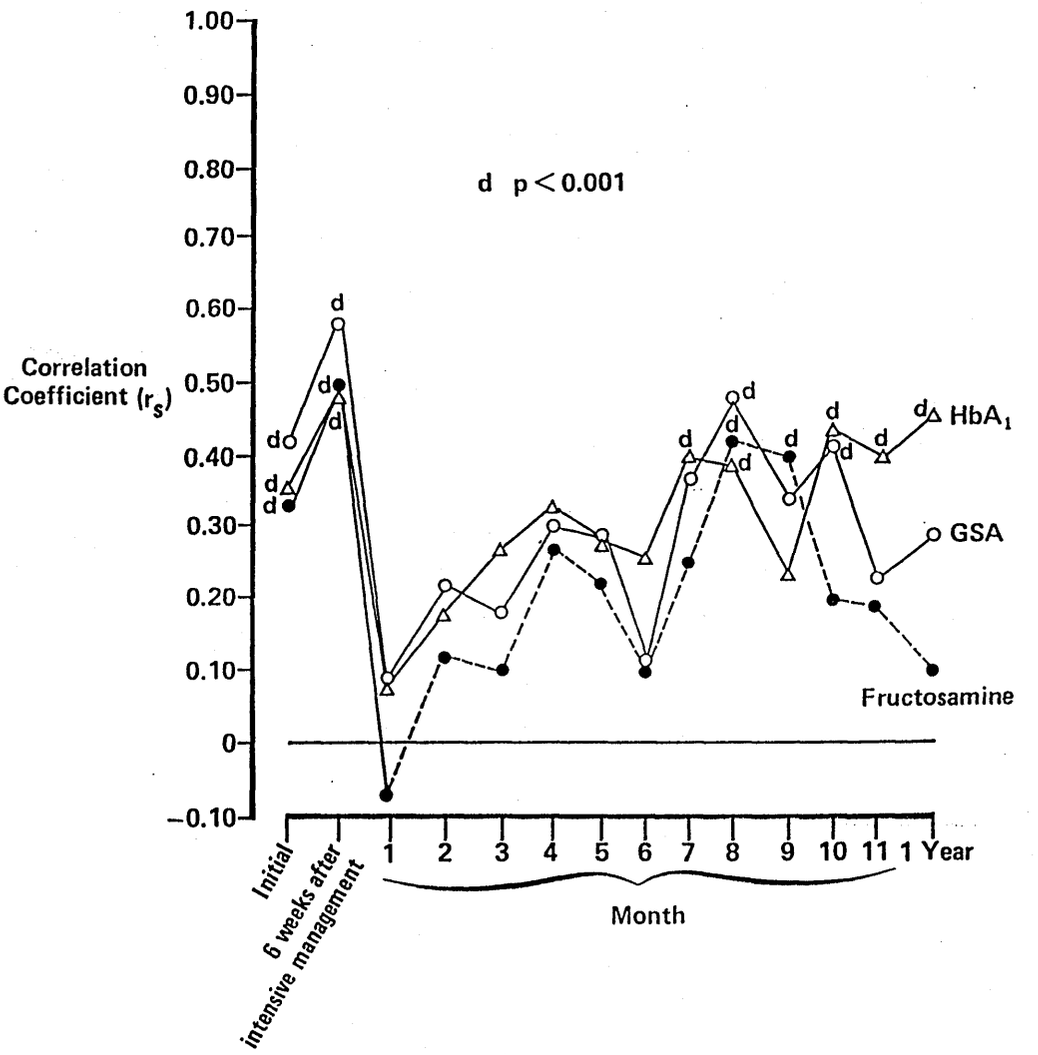


FIG. 34 Correlations between M values and glycosylated blood proteins over the course of 1 year.

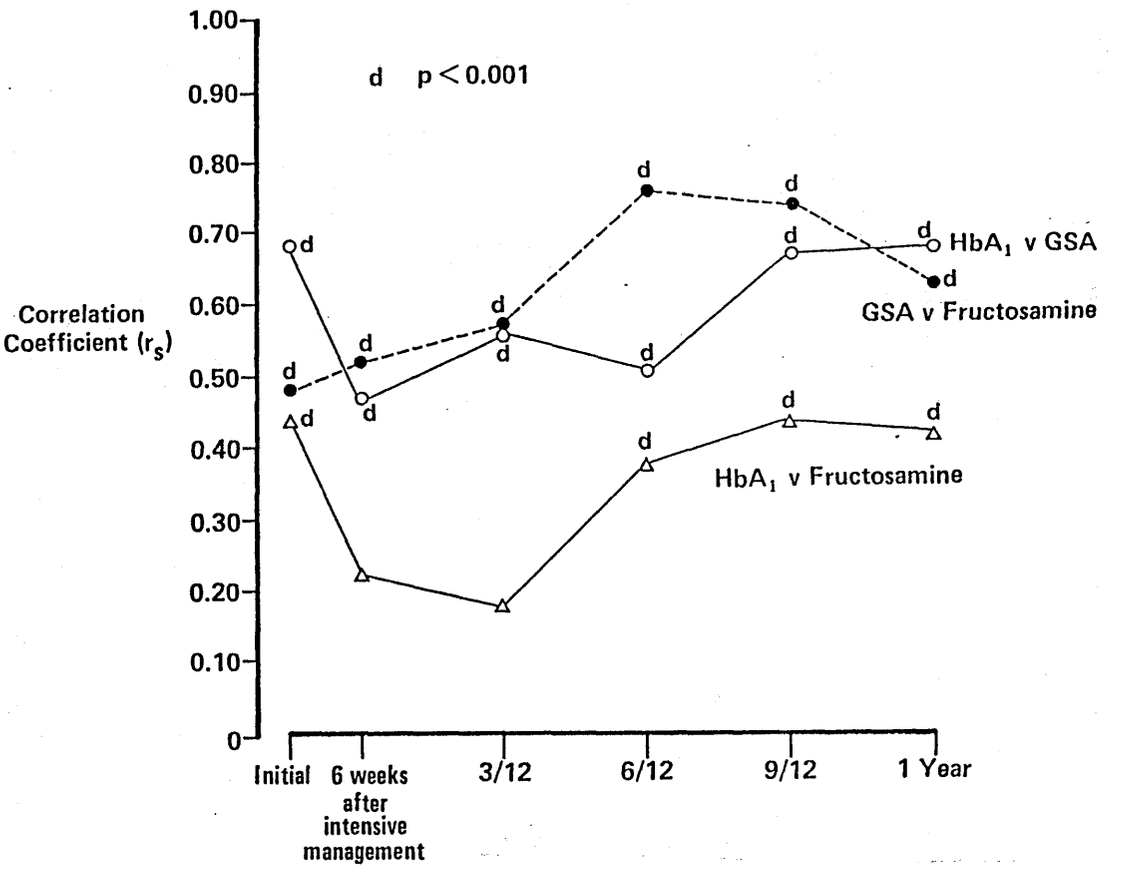


FIG. 35 Correlations between glycosylated blood proteins over the course of 1 year.

TABLE 65

Extent of agreement and disagreement between clinical control categories defined by HbA_1 and those defined by other measures of glycaemic control (%)

	BASELINE		POINT OF RANDOMISATION		3 MONTHS	6 MONTHS	9 MONTHS		1 YEAR	
Fructosamine										
Absolute Concordance	40		26		19	30	23		32	
Absolute Discordance	16		21		28	29	27		22	
GSA										
Absolute Concordance	49	**	47	**	37	40	42	**	44	**
Absolute Discordance	13		11		16	19	18		13	
Mean Blood Glucose										
Absolute Concordance	32		40	**	39	40	45		53	
Absolute Discordance	19		15		15	8	9		4	
M Values										
Absolute Concordance	30		40	**	33	38	43		58	
Absolute Discordance	20		16		17	12	10		4	

Values represent percentage agreement/disagreement

**p < 0.01 Significant Association by Kappa Cohen Analysis

TABLE 66

Extent of absolute agreement and disagreement between clinical control categories defined for GSA and fructosamine

	BASELINE	POINT OF RANDOMISATION	3 MONTHS	6 MONTHS	9 MONTHS	1 YEAR
Absolute Concordance	65 **	52 **	52 **	63 ***	58 **	56 **
Absolute Discordance	9	15	10	6	10	13

Values represent percentage agreement/disagreement

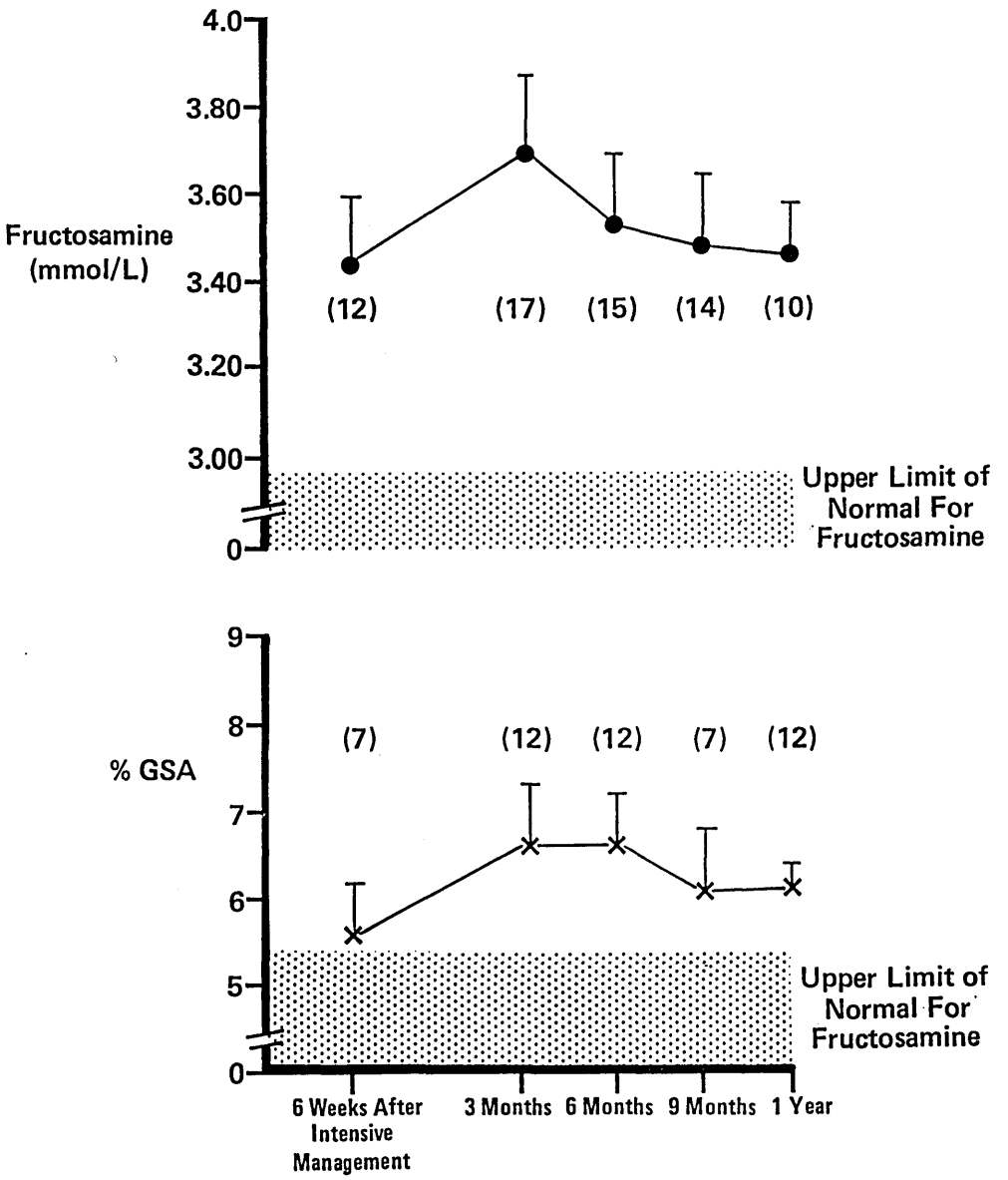
**p < 0.01 ***p < 0.001 significant association by Kappa Cohen Analysis

year (all $p<0.01$). Although the mean blood glucose values were discordant with HbA_1 levels on 4-19% of cases through the year,the only time when a significant agreement was observed was at the point of randomisation ($p<0.01$) owing to the smaller number of filter mean blood glucose values suitable for comparison thereafter. Likewise M values showed discordance with HbA_1 ranging from 4-20%, but associations were only significant at the point of randomisation and after 1 year ($p<0.01$), when glycaemic control was relatively more stable.

As expected, a closer relationship was observed between GSA and fructosamine at all time points although absolute discordance was observed in 6-15% of cases during the study (Table 66). However, at each time point the association between the 2 measures was significant ($p<0.01$ to 0.001).

4. Levels of glycaemia in patients with persistently normal HbA_1

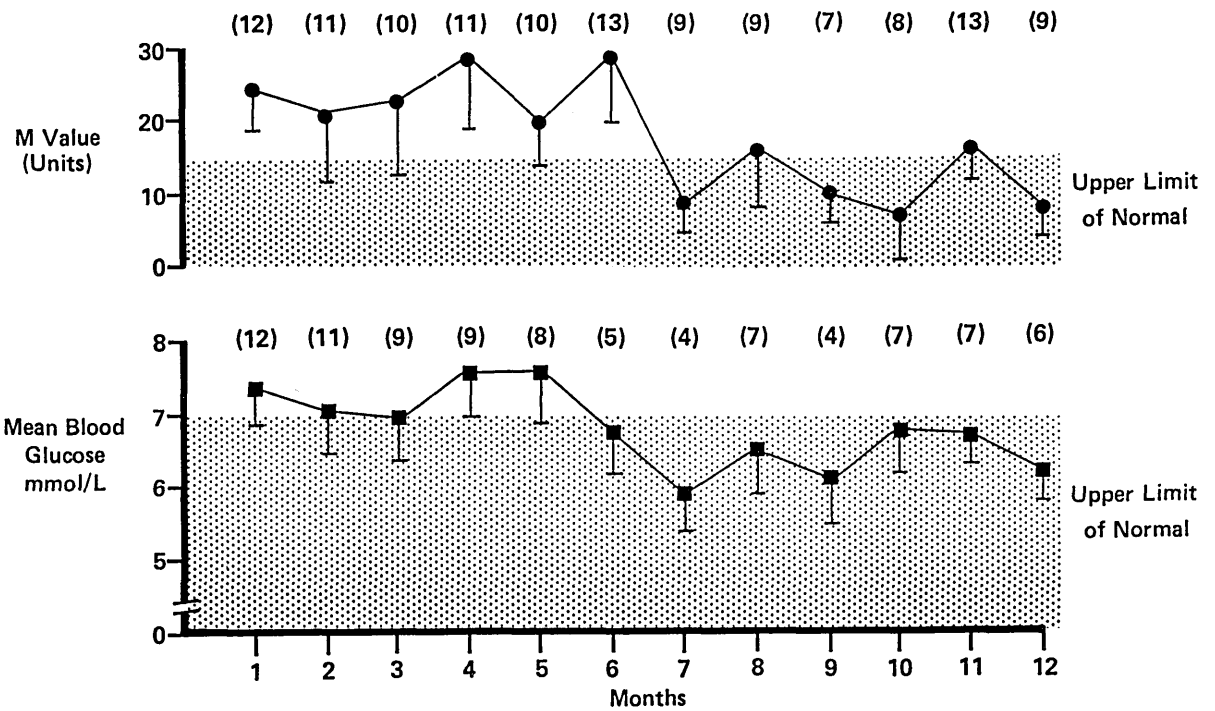
After the initial period of intensification of management, 57 of the original cohort had attained normal levels of HbA_1 (<8.0%),of whom 19 had levels within the normal range throughout the year. Using the same control criteria as in Table 64, I examined how frequently the other measures of glycaemia strayed into the fair or poor categories during the study. The pattern of the various measures of glycaemia is shown in Figures 36 and 37 and confirm that whilst mean blood glucose and M values frequently remained within the range for 'excellent' control, the mean GSA and fructosamine levels were never in the normal range. The number of patients with elevated values (i.e. fair or poor) for each glycaemia measure at different time points is also shown in Figures 36 and 37 and confirms that patients' fructosamine



Figures are number of patients with values outside normal range.

Mean ± SEM

FIG. 36 Fructosamine and GSA levels in 19 subjects with IDDM who had normal HbA_1 levels throughout the year.



Figures are number of patients with values outside normal range.

Mean ± SEM

FIG. 37 Levels of mean blood glucose and M values in 19 subjects with IDDM who had normal HbA_1 levels throughout the year.

values were most commonly outside the normal range, followed thereafter by GSA. With regard to the filter card mean blood glucose and M values, a distinct pattern was seen with less abnormal values recorded in the second half of the year.

3:4 HYPERTRIGLYCERIDAEMIA AND FRUCTOSAMINE

One unexpected finding from the cross-sectional analysis of the baseline data was that fructosamine levels appeared artificially lower in hypertriglyceridaemic (greater than 2.2mmol/l) subjects whereas if anything higher levels would have been anticipated since glycaemic control (assessed by GSA and fasting blood glucose) was not surprisingly somewhat poorer.

In the light of this finding and the subsequent observations on the limited role of fructosamine in reflecting short term improvements in glycaemia, I scrutinised the data more carefully at 6 weeks, 6 months and 1 year, when comprehensive measures of glycaemia and lipids were available. Of the 24 individual who were initially hypertriglyceridaemic, 9 were hyper-triglyceridaemic at least once during subsequent measurements, whilst 4 subjects remained persistently hypertriglyceridaemic throughout. In addition other patients developed hypertriglyceridaemia at different time points. Therefore between 11 and 15 of the 113 cases had triglyceride levels greater than 2.2mmol/l during the study.

Measures of glycaemic control were compared at the different time points in the normotriglyceridaemic and hypertriglyceridaemic sub-groups by Mann Whitney tests. Furthermore levels of GSA and fructosamine in the 2 groups were compared after correcting for differences in fasting blood glucose levels by analysis of

variance.

RESULTS

As expected, the hypertriglyceridaemic subjects generally had poorer glycaemic control, although only HbA_1 levels were significantly greater after 6 weeks of intensified management in those with hypertriglyceridaemia. However after taking into account the difference in fasting blood glucose levels, GSA was also significantly higher at 6 weeks in the hypertriglyceridaemic group. The most striking anomaly was the observation of reduced fructosamine levels in hypertriglyceridaemic sera, most notably at 6 months and 1 year (Table 67), although they were also lower after 6 weeks of intensified management when the difference in fasting blood glucose levels was taken into account.

TABLE 67

Measures of glycaemic control in hypertriglyceridaemic and normotriglyceridaemic subjects

	6 WEEKS INTENSIFIED MANAGEMENT		6 MONTHS		1 YEAR	
	HYPERTRIGLY-CERIDAEMIC	NORMOTRIGLY-CERIDAEMIC	HYPERTRIGLY-CERIDAEMIC	NORMOTRIGLY-CERIDAEMIC	HYPERTRIGLY-CERIDAEMIC	NORMOTRIGLY-CERIDAEMIC
NUMBER	12	87	11	88	15	84
TRIGLYCERIDES (mmol/l)	2.82 (2.31-19.39)	1.09 (0.34-2.09)	3.14 (2.54-58.90)	1.04 (0.19-2.14)	3.69 (2.54-11.89)	1.04 (0.29-2.19)
FASTING BLOOD GLUCOSE (mmol/l)	10.3 (1.3)	7.6 (0.8)	7.5 (0.8)	6.9 (0.4)	8.3 (1.1)	6.7 (0.4)
MEAN BLOOD GLUCOSE (mmol/l)	11.0 (1.2)	8.2 (1.0)	9.6 (1.1)	7.8 (0.4)	8.0 (0.6)	6.8 (0.2)
HbA_1 (%)	9.0 (0.5)$^{++*}$	7.9 (0.05)	7.9 (0.5)	8.2 (0.2)	8.2 (0.3)	8.2 (0.2)
GSA (%)	8.1 (1.1)$^{+}$	7.3 (0.3)	8.9 (1.0)	8.6 (0.4)	8.9 (1.1)	8.5 (0.4)
FRUCTOSAMINE (mmol/l)	3.24 (0.30)$^{+}$	3.52 (0.07)	3.24 (0.19)$^{+*}$	3.78 (0.09)	3.23 (0.23)$^{+*}$	3.80 (0.10)

$^{*}p < 0.05$

$^{+}p < 0.05$ Difference between groups account for difference

$^{++}p < 0.01$ in fasting blood glucose by analysis of variance

Figures are mean (SEM) or median (range)

1:5 DISCUSSION

The preceding series of studies demonstrates quite clearly that in IDDM, various measures of glycaemia give complementary rather than comparable information, particularly when metabolic control is less stable or changing. Support for this statement comes from the weak inverse correlation between C-peptide and measures of glycaemia. One explanation for the weak correlation is the relatively high percentage of patients who had no detectable endogenous insulin reserve, particularly since residual β cell function is thought to stabilise glycaemic control (v.i.) (551, 557).

In view of the recent introduction of the fructosamine assay into clinical practise, I was particularly interest to compare it with the established measures of glycaemia, as well as with the GSA assay that we had developed. I did not find that fructosamine values were altered either by varying albumin concentrations or by hypercholesterolaemia. However a consistent artefactual reduction in fructosamine levels was apparent in the presence of hypertriglyceridaemia, despite generally poorer glycaemic control in this group. The reason for this anomaly is not explained by the current series of experiments, but it is possible that lipaemic sera leads to NBT reduction early in the time course of the reaction with consequently less substrate available for the glycated protein bonds to reduce thereafter.

Throughout the study I found that on occasion GSA and fructosamine conveyed different information regarding glycaemic control, despite suggestions that the fructosamine reaction is predominantly due to activity of the ketoamine bonds of GSA.

Schleicher et al(23) found that 50% of the fructosamine value was derived from the measurement of unknown substance unrelated to glycated total serum proteins, and this important limitation may have been neglected in earlier studies.

In practice I found that only GSA was sensitive enough to detect improvements in glycaemic control after 2 weeks. Furthermore the relative magnitude of fall in GSA was much greater than that observed for either HbA_1 or fructosamine after 4 or 6 weeks. It was of interest to find that the cross-sectional relationship between measures of glycaemia varied quite considerably throughout the study. This explains the high discordance rate between HbA_1 and fructosamine and direct measures of glycaemia in particular. Perhaps the most damning evidence that fructosamine does not reflect predominantly GSA was the observation that absolute discordance (i.e. a normal level of one variable with an abnormal value for the other) was observed in up to 15% of comparisons.

Finally the observation of persistently normal HbA_1 levels despite elevated levels of GSA, fructosamine and direct measures of glycaemia confirms that HbA_1 is a relatively insensitive marker of hyperglycaemia in some individuals.

It would therefore seem that GSA is the most important measure of glycaemia in IDDM because of its sensitivity to both hyperglycaemic and hypoglycaemic states and that its use alongside HbA_1 is to be recommended in further longitudinal studies. The significance of the fructosamine assay clearly requires further investigation, particularly into its mechanism.

CHAPTER 6

ASPECTS AND DETERMINANTS OF CONTROL AND COMPLICATIONS

1:1. AUTONOMIC NEUROPATHY AND URINARY SODIUM AND ALBUMIN EXCRETION

Subjects: From the 205 insulin-dependent diabetic patients (153 trial patients and 52 controls), I identified 30 with definite cardiovascular autonomic neuropathy according to the criteria of Ewing and Clarke (694). All 30 patients had Valsalva ratios <1.10, immediate heart rate response to standing (30:15) ratio <1.00, and heart rate variations during deep breathing of <10 beats/minute. Of these, 20 (12M:8F) were matched in order of importance for sex, weight, age and duration of diabetes (to within 5 years), glycaemic control (to within 1% of HBA_1) and supine systolic blood pressure (to within 4 mmHg), with the same number of diabetics with normal cardiovascular autonomic tone (Valsalva ratio >1.21; 30:15 ratio >1.04, and heart rate variation during deep breathing >15 beats/minute). In addition 9 of the 20 diabetic patients with autonomic neuropathy had a postural fall in systolic blood pressure of more than 30 mmHg when adopting an erect from a supine posture, and a further 6 had a reduced diastolic blood pressure response (less than 10 mmHg) to handgrip dynamometry. Of the 20 subjects in each group, 17 had no detectable C-peptide resonse to a mixed meal. All patients in both groups showed negative Albustix tests for urinary protein and had normal serum urea and creatinine levels.

Table 68

CLINICAL AND BIOCHEMICAL FEATURES OF INSULIN-TREATED DIABETICS WITH OR WITHOUT AUTONOMIC NEUROPATHY.

	20 insulin-treated diabetics with Autonomic Neuropathy	20 insulin-treated diabetics without Autonomic Neuropathy
SEX RATIO M:F	12:8	12:8
AGE (YEARS)	48.8 (11.2)	48.6 (10.8)
AGE AT ONSET (YEARS)	33.3 (13.3)	31.9 (10.6)
DURATION OF DIABETES (YEARS)	15.6 (10.3)	16.8 (10.0)
BODY WEIGHT (Kg)	66.9 (20.8)	68.1 (14.1)
RETINOPATHY (NUMBER)	18 (B13,P5)	13 (B10,P3) *
PERIPHERAL NEUROPATHY (NUMBER)	16	13
ISCHAEMIC HEART DISEASE (NUMBER)	4	2
PERIPHERAL VASCULAR DISEASE (NUMBER)	10	4 *
FASTING BLOOD GLUCOSE (mmol/L)	12.3 (5.6)	9.9 (7.2)
MEAN BLOOD GLUCOSE (mmol/L)	12.6 (3.6)	12.2 (2.9)
M VALUE (UNITS)	119 (27-272)	117 (32-203)
URINARY GLUCOSE (mmol/24h)	110 (0.1-280.2)	206.1 (0.4-1020.0)
HbA_1 (%)	9.3 (1.5)	9.0 (1.6)

Figures are as stated, mean (SD) or mean (range)

* $p = 0.05$

Table 69

POSTURAL DIFFERENCES IN SYSTOLIC AND DIASTOLIC BLOOD PRESSURE IN INSULIN-TREATED DIABETICS WITH OR WITHOUT AUTONOMIC NEUROPATHY

	20 insulin-treated diabetics with Autonomic Neuropathy	20 insulin-treated diabetics without Autonomic Neuropathy
SUPINE	143 (18) / 83 (10)	145 (24) / 77 (10)
SEATED	130 (26) / 82 (8)	139 (23) * / 76 (12)
MEAN (SUPINE AND SEATED)	136 (24) / 82 (10)	143 (23) / 76 (10)
STANDING	128 (17) / 79 (7)	138 (27) * / 74 (11)

Figures refer to SYSTOLIC / DIASTOLIC MEAN (SD) BLOOD PRESSURE

* $p<0.05$

Results: Glycaemic control was comparable in the two groups. Diastolic blood pressure was suggestively higher in the patients with autonomic neuropathy irrespective of posture. Supine systolic blood pressures were comparable according to the study design, but both seating and standing systolic blood pressure values were lower in patients with autonomic neurpathy in whom the prevalence of peripheral vascular disease and diabetic retinopathy tended to be greater (both $p = 0.05$) (Tables 68 and 69). The daytime urine volume was significantly higher in the group without autonomic neuropathy ($p = 0.01$), whilst the night-time volume was higher in the group with autonomic neuropathy ($p<0.01$). There was no difference observed in the daytime sodium excretion rate, although nocturnal sodium excretion was significantly enhanced in those diabetics with autonomic neuropathy ($P<0.05$). The albumin excretion rates tended to be higher in those with autonomic neuropathy in the pooled 24 hour and daytime urine samples, and the difference in the overnight samples between the groups was significant ($p<0.02$), as was the nocturnal urinary albumin/creatinine ratio ($p<0.02$). The latter values confirmed that the urine collections in all cases were sufficiently accurate for analysis (Table 70).

Table 70

RENAL FUNCTION IN INSULIN-TREATED DIABETICS WITH AND WITHOUT AUTONOMIC NEUROPATHY

	20 insulin-treated diabetics with Autonomic Neuropathy	20 insulin-treated diabetics without Autonomic Neuropathy
SERUM UREA (mmol/L)	6.0 (1.7)	4.9 (1.1)
SERUM CREATININE (µmol/l)	82 (23)	79 (12)
CREATININE CLEARANCE (ml/min/1.73 sq.m)	129 (37)	129 (31)
DAYTIME URINE VOLUME (ml)	1545 (620-3200)	2106 (895-3000) *
NIGHT-TIME URINE VOLUME (ml)	830 (250-1550)	554 (160-1140) **
DAYTIME SODIUM EXCRETION (µmol/min)	153 (29-361)	171 (51-308)
NIGHT-TIME SODIUM EXCRETION (µmol/min)	229 (54-288)	96 (36-207) +
24 HR. ALBUMIN EXCRETION RATE (µg/min)	18.1 (1.0-56.7)	9.9 (2.3-38.0)
DAYTIME ALBUMIN EXCRETION RATE (µg/min)	20.5 (0.9-85.2)	11.3 (2.7-46.1)
NIGHT-TIME ALBUMIN EXCRETION RATE (µg/min)	13.2 (1.1-41.3)	5.8 (0.7-20.2) ++
DAYTIME ALBUMIN/ CREATININE RATIO	25 (3-107)	13 (3-39)
NIGHT-TIME ALBUMIN/ CREATININE RATIO	20 (3-86)	6 (1-25) ++

Figures are mean (SD) or mean (range)

+ $p < 0.05$ ++ $p < 0.02$ * $p = 0.01$ ** $p < 0.01$

1:2 RESIDUAL C-PEPTIDE SECRETION AND METABOLIC CONTROL

CROSS-SECTIONAL OBSERVATIONS

I was able to examine the relationship between residual C-peptide secretion and measures of glycaemia and lipid metabolism in all 205 insulin-treated diabetic patients (153 from the trial and the 52 controls). C-peptide was measured in response to a standard meal and patients classified as non-responders if levels were less than 0.02 pmol/ml, as low responders if levels were between 0.02 and 0.60 pmol/ml, and as high responders if levels were greater then 0.60 pmol/ml. In particular I investigated how important residual β cell function was in determining levels of HDL cholesterol and its subfractions, using analysis of variance and co-variance, controlling simultaneously for the effects of gender and C-peptide levels. Age, duration of diabetes, log transformed triglycerides, HbA1 and daily insulin dosage were included as co-variants.

RESULTS: The characteristics of the study population groups according to C-peptide status are shown in Table 71. The group with a high C-peptide response tended to be older ($p<0.06$) and contained relatively fewer men (N/S). Correction was made for the effects of age and gender in the analyses.

Although the high C-peptide response group had a shorter duration of diabetes and received less insulin in comparison to the non-responders ($p<0.001$), glycaemic control did not differ appreciably between the groups. Likewise body mass index, renal function, frequency of exercise and patterns of alcohol and tobacco consumption were similar in all groups.

The lipid and lipiprotein results are presented in Table 72.

Serum triglycerides tended to be higher in those patients with high C-peptide levels ($p<0.1$), and levels of apolipoprotein B and the mass ratio of LDL cholesterol to apolipoprotein B were suggestively lower in those with low C-peptide levels ($p<0.07$), but no significant differences were observed with regard to HDL cholesterol distribution, regardless of the method of isolation.

I further examined the role of C-peptide in explaining the variation in HDL cholesterol levels by univariate analysis but found no correlation between HDL and its subfractions and the C-peptide response, although significant correlations with serum triglycerides were recorded (Table 73). The individual contributions of various potential determinants of the HDL_{uc} cholesterol concentration, including the C-peptide response, were also tested by analysis of variance (Table 74). As expected, HbA_1 levels had a weak inverse relationship with C-peptide, and were positively associated with triglyceride levels. HDL cholesterol levels and its subfractions correlated closely with one another, regardless of the means of isolation. However, whilst serum triglyceride levels were negatively correlated with HDL cholesterol and its subfractions to a greater or lesser extent,no such association was demonstrated between HDL and either HbA1 or C-peptide.

Total serum HDL cholesterol was not explained by C-peptide levels, although gender exerted a significant effect, with higher HDL levels observed in women. The log triglyceride value also made a substantial contribution, leading to lower levels of HDL cholesterol. Likewise gender and triglyceride values were important determinants of the variation in HDL_2 cholesterol

levels, but persistant C-peptide secretion also exerted an effect, resulting in lower HDL_2 cholesterol levels. On the other hand, no significant predictors of HDL_3 cholesterol levels were found.

Table 71

CLINICAL CHARACTERISTICS OF PATIENTS GROUPED ACCORDING TO C-PEPTIDE STATUS

	NO C-PEPTIDE RESPONSE (<0.02pmol/ml)	LOW C-PEPTIDE RESPONSE (0.02-0.60pmol/ml)	HIGH C-PEPTIDE RESPONSE (>0.60pmol/ml)
No. of subjects	118	63	24
C-peptide (pmol/ml)	0.000 *** (0.000-0.017)	0.150 (0.020-0.570)	0.870 (0.680-1.430)
Age (years)	41.2 (1.3)	39.3 (1.7)	47.3 (3.2)
Sex Ratio (M:F)	75:43 (1.7:1)	42:21 (2.0:1)	11:13 (0.8:1)
BMI (Weight/ Height^2)	24.2 (0.3)	23.9 (0.5)	24.6 (1.0)
Duration of Diabetes (years)	18 (1) ***	9 (1)	6 (1)
Daily insulin dose (units/day)	54 (1) ***	51 (3)	34 (2)
HbA1 (%)	9.4 (0.2)	9.4 (0.2)	8.8 (0.4)
Fasting blood glucose (mmol/l)	11.3 (1.0)	10.4 (0.7)	8.3 (0.6)
Serum Creatinine (umol/l)	82 (4)	84 (3)	85 (4)
Alcohol intake +(units/week)	3.5 (0-30)	3.7 (0-60)	4.0 (0-24)
Regular exercise (%)	27	50	25

Figures are mean (SEM), median (range) or as stated

*** $p<0.001$

+ 1 unit = 10g ALCOHOL

Table 72

LIPIDS AND LIPOPROTEINS IN PATIENTS GROUPED ACCORDING TO C-PEPTIDE STATUS

	NO C-PEPTIDE RESPONSE	LOW C-PEPTIDE RESPONSE	HIGH C-PEPTIDE RESPONSE
Total cholesterol (mmol/l)	5.76 (0.14)	5.73 (0.20)	5.59 (0.27)
Total triglycerides (mmol/l)	1.29 (0.36-4.34)	1.29 (0.39-23.29)	1.55 (0.49-5.40)
LDL cholesterol (mmol/l)	3.70 (0.13)	3.73 (0.19)	3.64 (0.24)
Apolipoprotein B (mg/dl)	110 (3)	99 (3)	111 (5)
LDL cholesterol+ apolipoprotein B	1.35 (0.05)	1.52 (0.08)	1.35 (0.11)
HDL_{uc} cholesterol	1.43 (0.03)	1.48 (0.05)	1.47 (0.07)
HDL_{pt} cholesterol	1.38 (0.05)	1.37 (0.07)	1.36 (0.10)
HDL_{2uc} cholesterol	0.70 (0.03)	0.75 (0.07)	0.68 (0.05)
HDL_{2pt} cholesterol	0.70 (0.05)	0.73 (0.07)	0.65 (0.11)
HDL_{3uc} cholesterol	0.73 (0.02)	0.73 (0.03)	0.78 (0.07)
HDL_{uc}/LDL cholesterol	0.44 (0.02)	0.47 (0.03)	0.46 (0.04)
HDL_{uc}/total cholesterol	0.26 (0.01)	0.27 (0.01)	0.27 (0.01)

Figures are mean (SEM) or median (range)
+LDL cholesterol converted to mg/dl for calculation of ratio
HDL_{uc} refers to ultracentrifugation
HDL_{pt} refers to precipitation data.

TABLE 73

Spearman correlation coefficients of C-peptide, HbA_1, log triglycerides and HDL cholesterol and its subfractions in 205 subjects with IDDM

	C PEPTIDE	HDL_{uc} CHOLESTEROL	HDL_{pt} CHOLESTEROL	HDL_{2uc} CHOLESTEROL	HDL_{2pt} CHOLESTEROL	Log TRIGLYCERIDES
HDL_{uc} CHOLESTEROL	-0.06	----	----	----	----	----
HDL_{pt} CHOLESTEROL	-0.03	0.82***	----	----	----	----
HDL_{2uc} CHOLESTEROL	-0.09	0.92***	0.76***	----	----	----
HDL_{2pt} CHOLESTEROL	-0.06	0.81***	0.80***	0.82***	----	----
Log TRIGLYCERIDES	0.13	-0.30***	-0.47***	-0.28**	-0.42***	----
HbA_1	-0.16*	-0.10	-0.14	-0.07	-0.13	0.27**

Figures are Spearman correlation coefficients (r_s)

*p < 0.05 **p < 0.01 ***p < 0.001

Table 74

POTENTIAL DETERMINANTS OF HDL CHOLESTEROL AND ITS SUBFRACTIONS

USING ANALYSIS OF VARIANCE

(a) HDL CHOLESTEROL LEVELS

MAIN EFFECTS	F	Significance of F
C-PEPTIDE	2.398	0.094
GENDER	12.467	0.001 ***
CO-VARIATES		
DURATION OF DIABETES	1.305	0.255
AGE	0.099	0.754
Log. TRIGLYCERIDE	9.458	0.002 ***
DAILY INSULIN DOSAGE	0.158	0.692
HbA_1	0.351	0.555

(b) HDL_2 CHOLESTEROL LEVELS

MAIN EFFECTS	F	Significance of F
C-PEPTIDE	3.511	0.032 *
GENDER	25.481	0.001 ***
CO-VARIATES		
DURATION OF DIABETES	2.799	0.096
AGE	0.016	0.900
Log. TRIGLYCERIDE	10.906	0.001 ***
DAILY INSULIN DOSAGE	1.415	0.236
HbA_1	0.000	0.996

(c) HDL_3 CHOLESTEROL LEVELS

MAIN EFFECTS	F	Significance of F
C-PEPTIDE	0.937	0.394
GENDER	0.858	0.356
CO-VARIATES		
DURATION OF DIABETES	0.133	0.716
AGE	0.127	0.722
Log. TRIGLYCERIDES	0.177	0.675
DAILY INSULIN DOSAGE	0.631	0.428
HbA_1	0.559	0.456

1:3 RESIDUAL C-PEPTIDE SECRETION AND METABOLIC CONTROL

LONGITUDINAL OBSERVATIONS

Following the observations on all 205 subjects at initiation to the study, I then proceeded to examine prospectively whether residual post-prandial C-peptide secretion modified metabolic control during the 1st year of the home blood glucose monitoring study. The same criteria for non-responders and low and high C-peptide responders (<0.020, 0.020-0.600, >0.600 pmol/ml, respectively) were used to classify the 147 subjects who reached the point of randomisation. All subjects had serum creatinine levels less than 140 μmol/l.

Results: The characteristics of the patients classified according to the C-peptide response at entry to the study are shown in Table 75. 70 (48%) of patients had undetectable C-peptide following a standardised mixed meal, 57 (38%) had a low C-peptide response, and 20 (14%) a high C-peptide response. The three groups were similar to one another with regard to body mass index, frequency of exercise and patterns of alcohol and tobacco consumption. The daily insulin dose and duration of diabetes was least in the group with a high C-peptide response ($P<0.001$), but although they tended to be older and the group composed of relatively fewer men, gender distribution or the age difference between the groups did not differ significantly. Daily insulin dosage remained significantly lower in the group with a high C-peptide response throughout the study ($P<0.001$).

Glycaemic Control. HbA_1 fell significantly from initial levels during the study in all 3 groups to a greater or lesser degree.

However whilst levels in the C-peptide negative and low C-peptide responsive groups remained virtually identical, the high C-peptide responder group had persistently lower levels throughout the year following the 6 week period of intensified management (Figure 38).

GSA levels fell significantly during the study in the low or negative C-peptide responsive groups, but appeared more variable in the high C-peptide responsive group. GSA levels remained least in the high C-peptide responders, intermediate in the low C-peptide responders and highest in the C-peptide negative group at all times during the study with the exception of 6 months when mean levels were identical in the low and negative C-peptide responders (Figure 39).

Fructosamine levels varied much more than the other measured glycated blood proteins. Levels only altered appreciably with time in the C-peptide negative group and were similar in the low and high C-peptide responder at most time points. Fructosamine levels generally remained highest in the C-peptide negative group with the exception of the 3 month time point, and were significantly higher at baseline and after 2 and 4 weeks and 9 and 12 months (Figure 40).

Fasting blood glucose levels were higher in the C-peptide negative group initially, falling with time, and mean blood glucose fell significantly with time in all groups. Thereafter mean blood glucose levels remained slightly higher in the C-peptide negative group with a significant difference observed at 12 months (Figure 41).

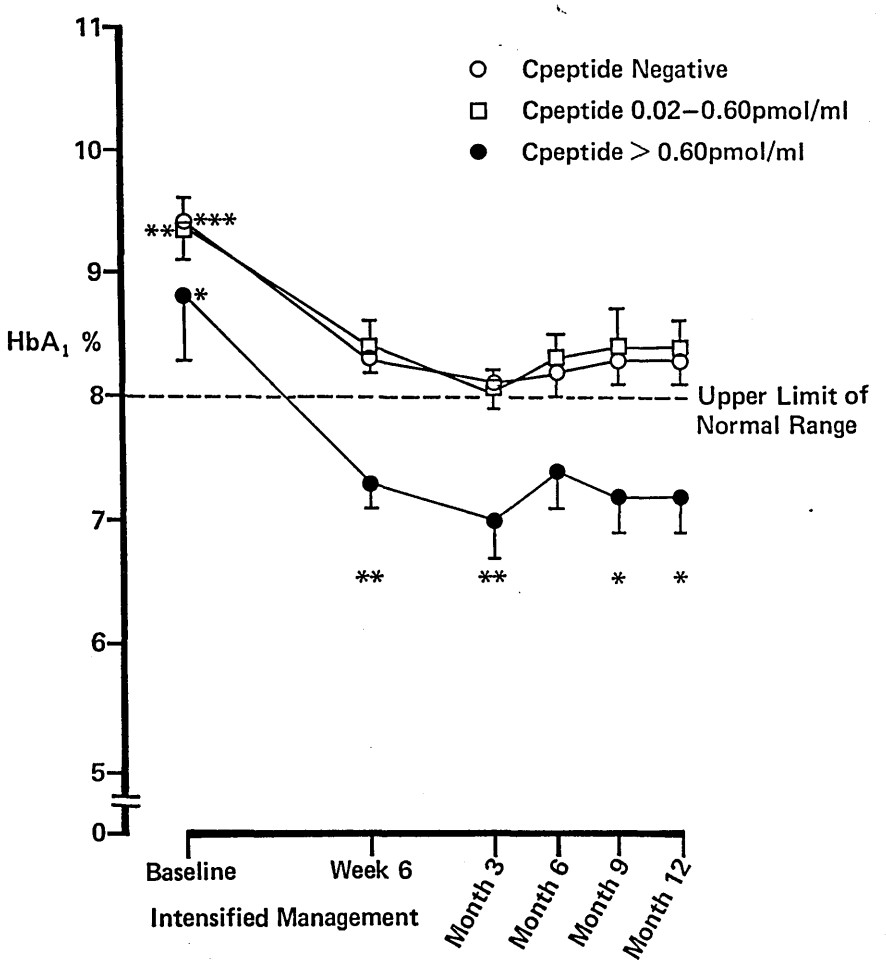


FIG. 38 Changes in HbA_1 during home blood glucose monitoring study according to C-peptide status.

Figures represent Mean ± SEM

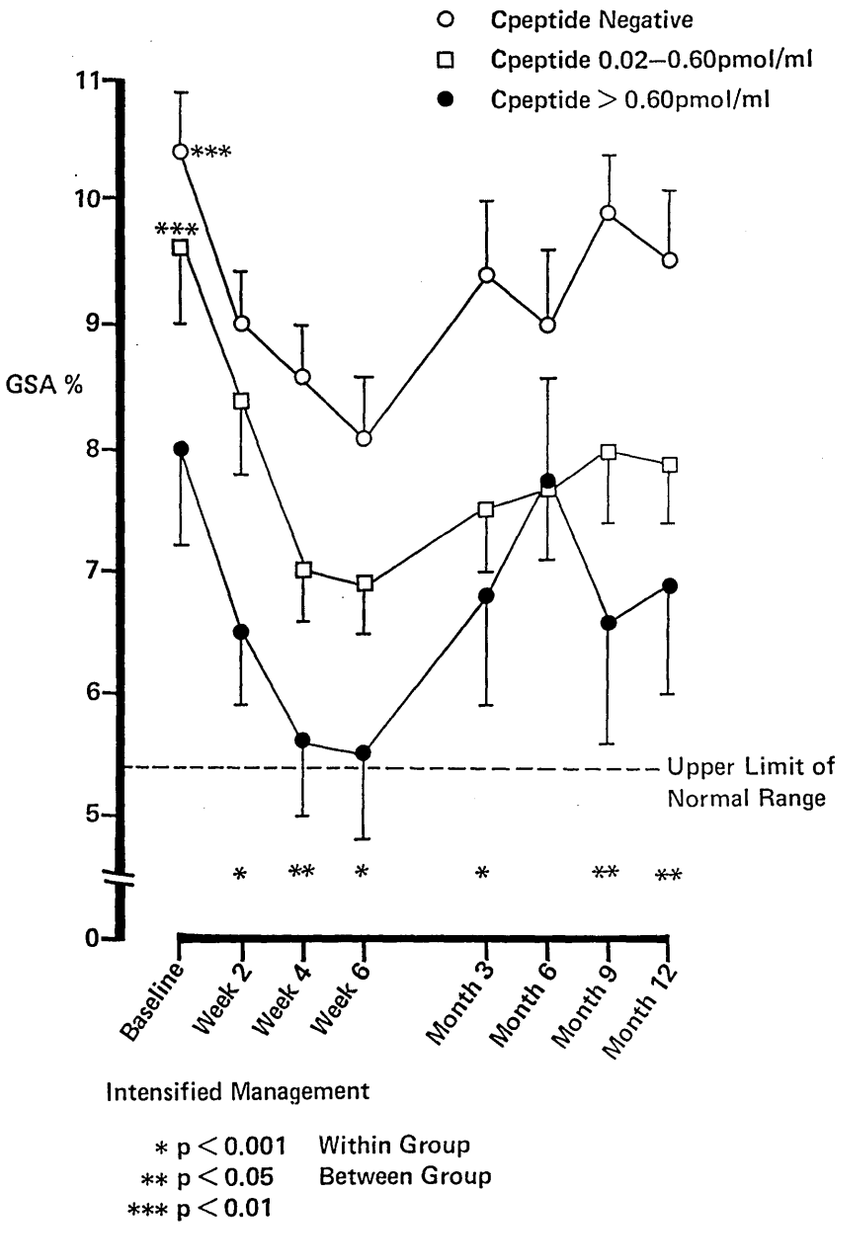


FIG. 39 **Changes in GSA during home blood glucose monitoring study according to C-peptide status.**

Figures represent Mean ± SEM

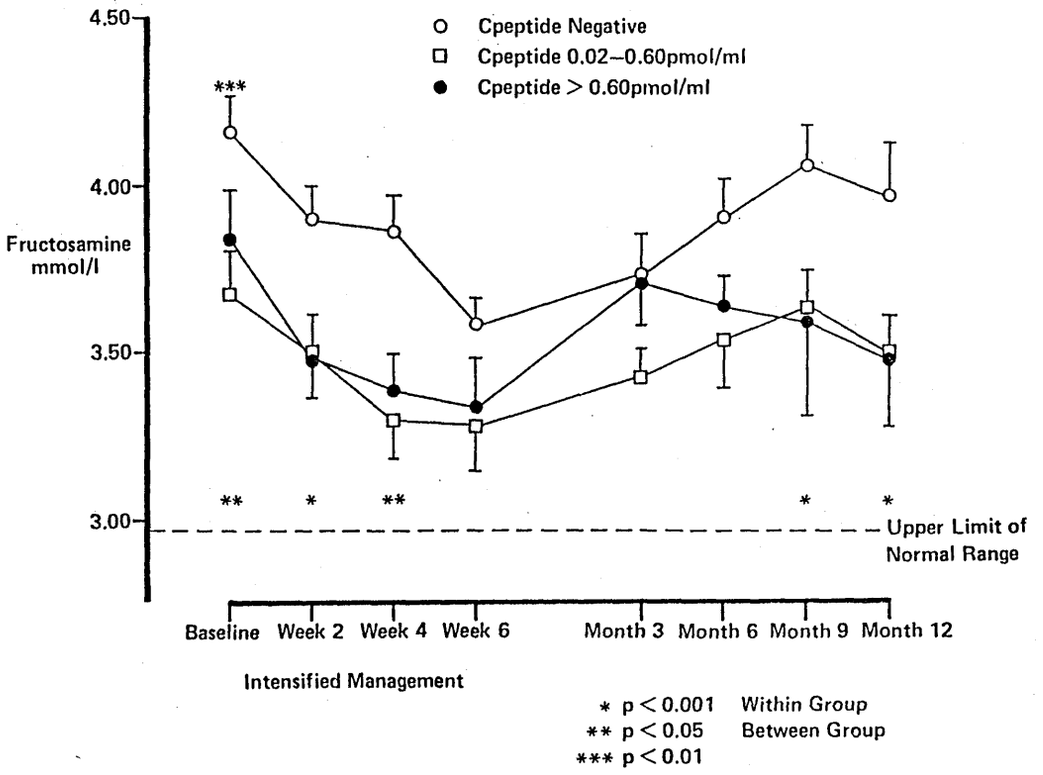


FIG. 40 Changes in fructosamine during home blood glucose monitoring study according to C-peptide status.

Figures represent Mean ± SEM

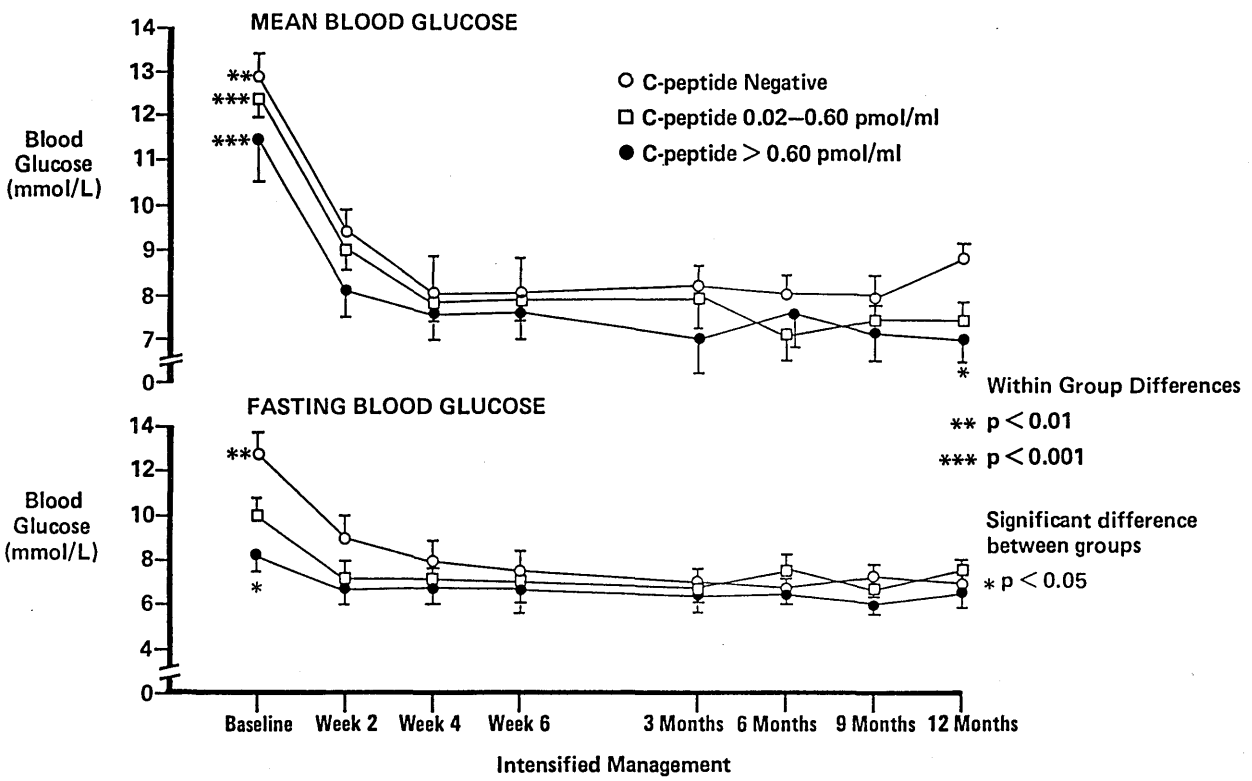


FIG. 41 Changes in fasting and mean blood glucose levels during home blood glucose monitoring study according to C-peptide status.

Figures represent Mean ± SEM

Lipids and Lipoproteins. There were no differences in levels of triglycerides and total LDL and HDL cholesterol, in addition to the HDL_2 and HDL_3 cholesterol subfractions or apolipoprotein B between the groups at any point during the study (Figure 42, Table 76). However, the levels of HDL_2 and HDL_3 cholesterol fractions did change appreciably during the year within the groups (Table 76).

Table 75

INITIAL CLINICAL CHARACTERISTICS OF 147 PATIENTS WITH INSULIN-INDEPENDENT DIABETES CLASSIFIED ACCORDING TO C-PEPTIDE RESPONSE TO A MIXED MEAL

	C-PEPTIDE NEGATIVE (<0.020pmol/ml)	LOW C-PEPTIDE RESPONDERS (0.020-0.600pmol/ml)	HIGH C-PEPTIDE RESPONDERS (>0.600pmol/ml)
No. of sujects	70	57	20
Sex Ratio (M:F)	45:25 (1.8:1.0)	40:17 (2.0:1.0)	10:10 (1.0:1.0)
Age (years)	40 (2)	40 (2)	47 (4)
BMI (Weight/ Height^2)	23.6 (0.3)	23.5 (0.5)	23.9 (1.0)
Duration of Diabetes (years)	18 (1)***	9 (1)	6 (1)
Daily insulin dose (units/day)	57 (2)	49 (3)	32 (2) ***
Alcohol intake (units/week)	3.5 (0-30)	3.7 (0-60)	4.0 (0-24)
Smokers (%)	49	44	42
Regular exercise	43	54	25

*** $p<0.001$

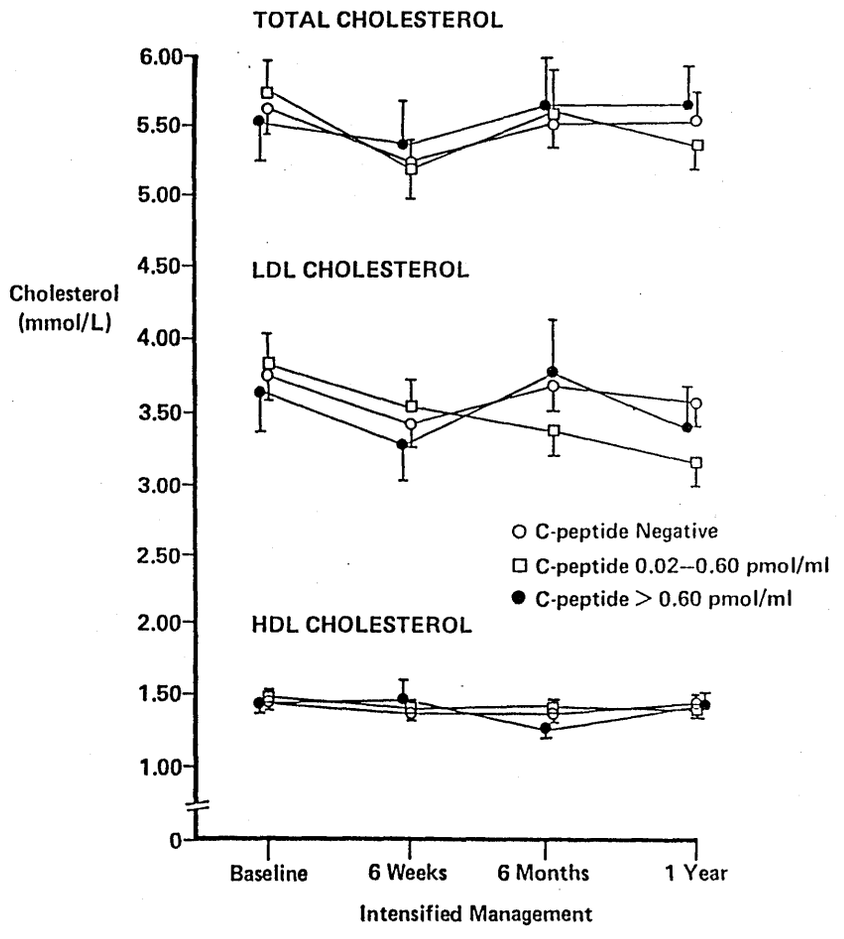


FIG. 42 Changes in plasma total, HDL and LDL cholesterol levels during home blood glucose monitoring study according to C-peptide status.

Figures represent Mean ± SEM

Table 76

LIPID AND LIPOPROTEIN LEVELS OVER THE COURSE OF STUDY IN PATIENTS WITH IDDM CLASSIFIED ACCORDING TO THE C-PEPTIDE RESPONSE TO A MIXED MEAL

	C-PEPTIDE NEGATIVE (<0.02pmol/ml)	LOW C-PEPTIDE RESPONDERS (0.02-0.60pmol/ml)	HIGH C-PEPTIDE RESPONDERS (>0.6pmol/ml)
TRIGLYCERIDES (mmol/l)			
BASELINE	1.24 (0.36-4.24)	1.21 (0.39-23.29)	1.55 (0.49-4.40)
6 WEEKS INTENSIFIED MANAGEMENT	1.09 (0.24-2.94)	1.10 (0.34-19.34)	1.25 (0.29-3.24)
6 MONTHS	1.12 (0.19-3.14)	1.04 (0.24-58.90)	1.63 (0.29-3.74)
1 YEAR	1.09 (0.39-8.90)	1.19 (0.29-11.89)	1.24 (0.44-3.69)
APOLIPOPROTEIN B (mg/dl)			
BASELINE	102 (3)	97 (3)	110 (5)
6 WEEKS INTENSIFIED MANAGEMENT	100 (3)	99 (3)	109 (5)
6 MONTHS	102 (3)	103 (4)	107 (5)
1 YEAR	104 (3)	103 (4)	102 (5)
HDL_2 CHOLESTEROL (mmol/l)			
BASELINE	0.73 (0.03)	0.76 (0.05)	0.64 (0.06)*
6 WEEKS INTENSIFIED MANAGEMENT	0.73 (0.04)	0.76 (0.05)	0.85 (0.09)
6 MONTHS	0.70 (0.04)	0.76 (0.05)	0.60 (0.06)
1 YEAR	0.73 (0.04)	0.67 (0.04)	0.76 (0.08)
HDL_3 CHOLESTEROL (mmol/l)			
BASELINE	0.72 (0.03)**	0.71 (0.03)**	0.79 (0.06)*
6 WEEKS INTENSIFIED MANAGEMENT	0.65 (0.03)	0.63 (0.03)	0.63 (0.07)
6 MONTHS	0.69 (0.03)	0.65 (0.05)	0.69 (0.03)
1 YEAR	0.73 (0.03)	0.75 (0.03)	0.69 (0.04)

*p<0.05 **p<0.01 Within group differences.
Figures are mean (SEM) or median (range).

1:4 RESIDUAL C-PEPTIDE SECRETION IN LONGSTANDING IDDM AND COMPLICATIONS

I examined whether or not residual C-peptide secretion had any bearing on the prevalence and evolution of complications in IDDM. Because diabetic complications rarely present themselves early in the course of the disease, only subjects whose duration of diabetes exceeded 6 years were eligible for comparison. Furthermore, because of this factor and suggestions that the absolute age of the patient might be relevant, I selected 2 groups of patients with and without C-peptide secretion who were matched in order of importance for age and duration of diabetes (to within 5 years in all cases), and body mass index (to within 1 unit in all cases).

Of the 147 subjects randomised to take part in the 2 year study, 70 (48%) had no detectable C-peptide reponse to a mixed meal, of whom 31 (23 men) were suitably matched with 31 (20 men) with residual β cell function.

RESULTS: The clinical characteristics of the 31 subjects in each group are shown in Table 77. The median stimulated C-peptide level in the C-peptide secretor group was 0.090 pmol/ml, of whom 20 had levels less than or equal to 0.200 pmol/ml. In addition to age, duration of diabetes and body mass index, the two groups did not differ with respect to daily insulin dosage or insulin species, patterns of tobacco or alcohol consumption, number of patients previously treated with oral hypoglycaemics or who had experienced diabetic ketoacidosis, or insulin antibody

titres. Furthermore patterns of urinary albumin and total protein excretion were similar, although serum creatinine levels were greater in the C-peptide secretory group ($p<0.05$) (Tables 77 and 78).

Glycaemic Control and C-peptide Secretion. Following trial entry, an appreciable and sustained improvement in HbA_1 and mean blood glucose was observed in both groups ($p<0.01$), with less impressive reductions in GSA and fructosamine. HbA_1, fructosamine, GSA and to a lesser extent mean blood glucose values, generally remained higher in the C-peptide negative group throughout the year and the difference in GSA levels was significant at 3 and 6 months ($p<0.05$) (Figures 43 and 44).

No significant difference in insulin dose, insulin antibody titre or body mass index was apparent after 1 year (Table 79). However 2 individuals who were initially categorised as C-peptide negative (<0.020 pmol/ml) had detectable C-peptide levels (0.028 and 0.038 pmol/ml) after 1 year. In contrast 7 individuals who secreted C-peptide initially had no detectable C-peptide response to a mixed meal after 1 year. The C-peptide level fell slightly overall from a median level of 0.090 to 0.068 pmol/ml. Of the 7 subjects with residual C-peptide secretion initially but not after 1 year, 5 initially had levels less than 0.060 pmol/ml, whilst the levels of trial entry of the remaining two were 0.100 and 0.360 pmol/ml. Glycaemic control in these 7 patients was persistently worse than the C-peptide secretor group as a whole, with mean levels of HbA_1, GSA and fructosamine greater than the mean value plus 2 standard errors for all these parameters for

the complete C-peptide responsive group throughout the year.

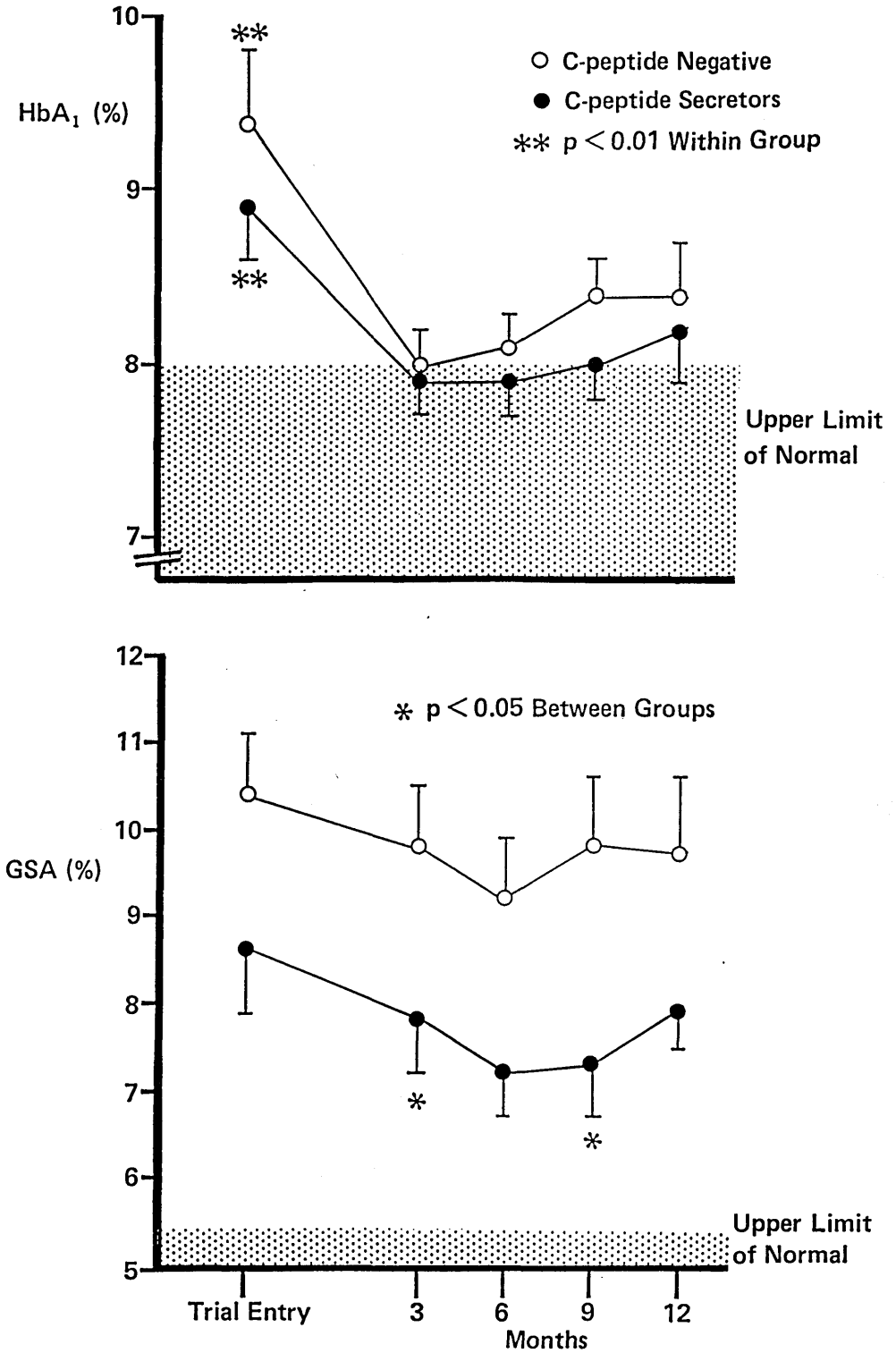


FIG. 43 Glycaemic control over 1 year assessed by HbA_1 and GSA in 31 insulin dependent diabetics with or without detectable C-peptide secretion at entry to the study.

Figures represent Mean ± SEM

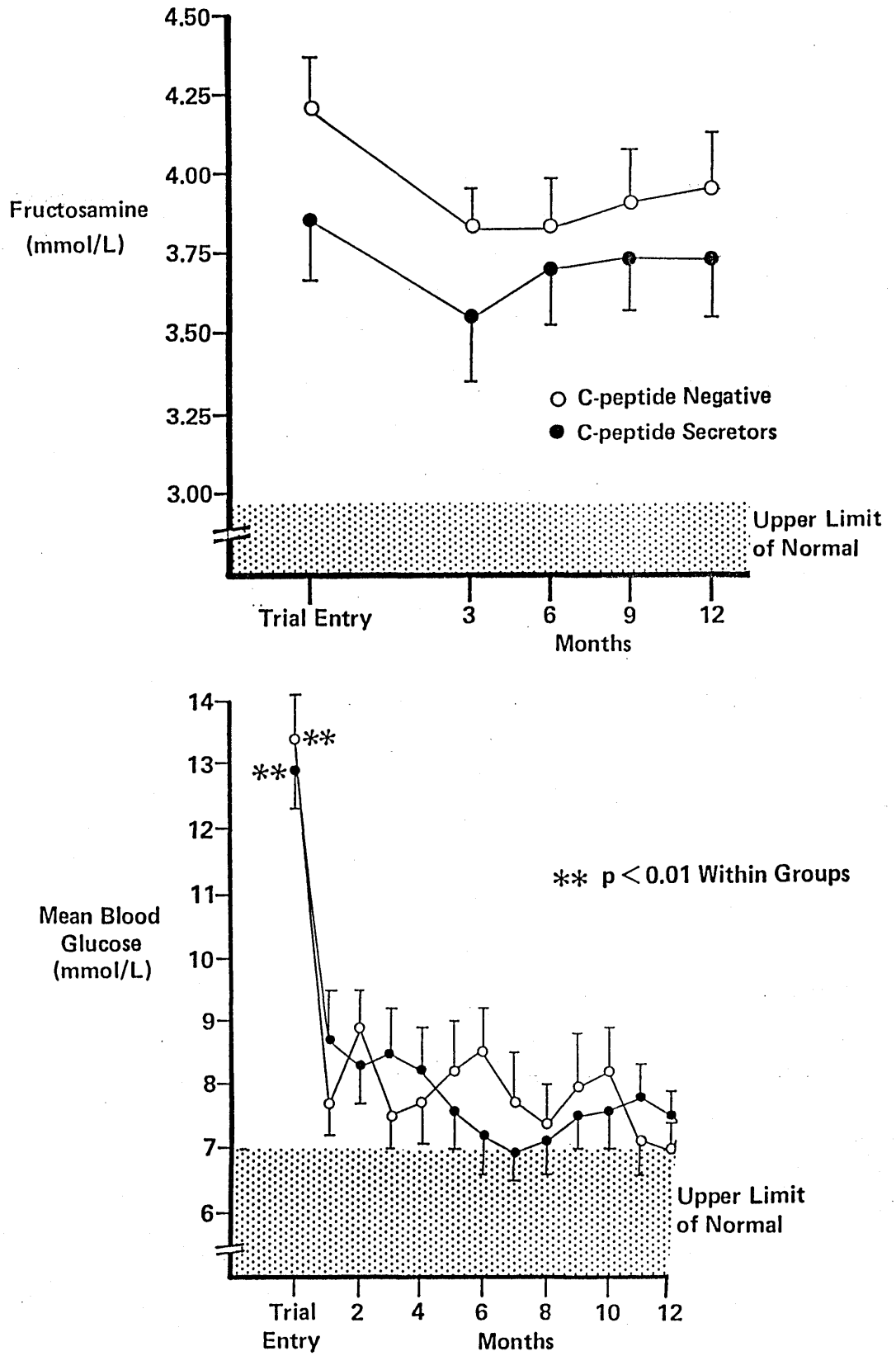


FIG. 44 Glycaemic control over 1 year assessed by fructosamine and monthly mean blood glucose values in 31 insulin dependent diabetics with or without detectable C-peptide secretion at entry to the study.

Figures represent Mean ± SEM

Table 77

CHARACTERISTICS OF TWO GROUPS OF INSULIN-DEPENDENT DIABETIC PATIENTS WITH AND WITHOUT CIRCULATING C-PEPTIDE MATCHED FOR AGE, DURATION OF DIABETES AND BODY MASS INDEX AT ENTRY TO THE STUDY

	C-PEPTIDE NEGATIVE GROUP	C-PEPTIDE SECRETOR GROUP
Number (men)	31 (23)	31 (20)
C-peptide levels (pmol/ml)	0.000 (0-0.015)	0.090 (0.020-1.200)
Age (years)	41.7 (2.5) (18-64)	42.8 (2.5) (16-62)
Duration of Diabetes (years)	15.0 (1.4) (6-32)	15.4 (1.5) (6-33)
BMI (Weight/ Height^2)	23.6 (0.6)	24.0 (0.5)
Daily insulin dosage (units)	58 (3)	53 (3)
Type of insulin (number) x	16B 15H	17B 14H
Previous diabetic Ketoacidosis (No.)	23	18
Previous oral hypoglycaemic therapy (No.)	11	11
Smokers (number)	10	12
Alcohol (units/week)	3 (0-30)	6 (0-60)
Insulin Antibodies (binding units)		
BOVINE	20.0 (5.2-104.0)	16.5 (6.4-240.0)
HUMAN	18.8 (4.4-97.0)	17.0 (4.4-206.0)
Serum creatinine (µmol/l)	79 (3)	87 (3)*

Figures are mean (SEM), median (range) * $p<0.05$
x B = Beef H = Human

Table 78

PREVALENCE OF SPECIFIC COMPLICATIONS AND RELATED BIOCHEMISTRY AT TRIAL ENTRY AND AFTER 1 YEAR IN TWO GROUPS OF INSULIN-DEPENDENT DIABETIC PATIENTS WITH AND WITHOUT CIRCULATING C-PEPTIDE AT TRIAL ENTRY

	C-PEPTIDE NEGATIVE GROUP		C-PEPTIDE SECRETOR GROUP	
	TRIAL ENTRY	AFTER 1 YR.	TRIAL ENTRY	AFTER 1 YR.
No. of subjects	31	27	31	27
Retinopathy (number)	10B 11P	8B 10P	18B 5P	10B 10P
Peripheral neuropathy score	12.5 (0.7)	12.3 (0.7)	12.2 (0.5)	12.0 (0.7)
Autonomic neuropathy score	2.6 (0.4)	2.2 (0.5)	2.5 (0.5)	2.9 (0.4)
Albumin excretion rate (µg/minute)	7.2 (2.4-536.1)	9.1 (1.4-1193.3)	6.6 (0.3-229.9)	5.6 (1.1-187.3)
Urinary protein excretion	0.05 (0.05-1.00)	0.20 (0.05-2.00)	0.05 (0.05-1.00)	0.10 (0.50-1.90)
Microalbuminuria (number)	6	6	5	3
Overt nephropathy (number)	4	3	2	1
Serum creatinine (µmol/l)	79 (3)	84 (3)	87 (3)*	87 (3)
Hypertension (number)	6	7	5	5
Ischaemic heart disease (number)	3	2	3	3
Peripheral vascular disease (number)	1	1	6*	5

Figures are mean (SEM), median (range)
* $p < 0.05$ between groups

Glycaemic control was particularly poor for the two patients with initially high C-peptide levels (0.100 and 0.360 pmol/ml) and their mean GSA levels during the year averaged 10.0% and 13.6% respectively. Consequently, those subjects with persistant C-peptide secretion after 1 year achieved significantly better glycaemic control in comparison to the C-peptide negative group (data not shown).

Table 79

C-PEPTIDE LEVELS, BODY MASS INDEX, INSULIN DOSE, AND INSULIN ANTIBODY TITRES AFTER 1 YEAR IN 27 SUBJECTS WITH OR WITHOUT C-PEPTIDE SECRETION AT TRIAL ENTRY

	C-PEPTIDE NEGATIVE GROUP	C-PEPTIDE SECRETOR GROUP
C-peptide (pmol/ml)	0.000 (0-0.038)	0.068 (0-1.190)
Change in C-peptide status (number)	2	7
BMI (Weight/ Height^2)	24.4(0.6)	24.8(0.5)
Daily Insulin Dose (units)	57 (3)	55 (4)
Insulin Antibody (binding units)		
BOVINE	15.1 (3.1-200.0)	17.3 (4.4-132.0)
HUMAN	16.8 (2.8-86.0)	15.5 (4.2-116.0)

Figures are Mean (SEM), Median (range).

Complications. The prevalence of complications and related biochemistry in the two groups at trial entry and after 1 year is shown in Table 78.

Peripheral vascular disease and background retinopathy were more frequently detected in the C-peptide secretor group, whilst proliferative retinopathy was more prevalent in the C-peptide negative group ($p<0.05$) at entry to the trial. There was no difference in the prevalence of hypertension, nephropathy, microalbuminuria or ischaemic heart disease, nor in the peripheral or autonomic neuropathy scores.

27 subjects from each group completed the 1st year of the study. In the group with a detectable C-peptide response initially, one subject with peripheral vascular disease, nephropathy, hypertension, autonomic neuropathy and background retinopathy underwent a below knee amputation and was withdrawn from the trial. Of the remaining three who all defaulted from follow up, one had definite peripheral neuropathy and proliferative retinopathy but 2 were free of complications.

In the group without C-peptide secretion one individual with hypertension, ischaemic heart disease, nephropathy, autonomic neuropathy and proliferative retinopathy died following a myocardial infarction. One further drop out from this group had peripheral and autonomic neuropathy and background retinopathy and the other two were free of complications. Consequently whilst the prevalence of peripheral vascular disease after 1 year remained greater in the group with persistant C-peptide secretion, the difference was no longer significant.

In addition, because of the progression of retinopathy, the prevalence of all other complications (including retinopathy) was similar in both groups after 1 year, and peripheral and autonomic neuropathy scores and urinary albumin and protein excretion was similar in both groups.

I also categorised subjects initially and after 1 year, on the basis of whether they had any significant microvascular disease (microalbuminuria, overt nephropathy or proliferative retinopathy), but the prevalence in the groups remained similar on both occasions. Furthermore when other individuals who only had autonomic neuropathy and/or peripheral neuropathy and/or macrovascular disease were included in the comparison the prevalence of any complication in the 2 groups remained remarkably similar (Table 80).

Table 80

PREVALENCE OF ANY MICROVASCULAR (+ NEUROPATHIC)(+MACROVASCULAR) COMPLICATIONS AT TRIAL ENTRY AND AFTER 1 YEAR IN TWO GROUPS OF PATIENTS WITH IDDM WITH AND WITHOUT CIRCULATING C-PEPTIDE AT TRIAL ENTRY

	TRIAL ENTRY		AFTER 1 YEAR	
	C-PEPTIDE NEG. GROUP	C-PEPTIDE SEC. GROUP	C-PEPTIDE NEG. GROUP	C-PEPTIDE SEC. GROUP
MICROVASCULAR COMPLICATIONS (microalbuminuria (and/or persistant (proteinuria and/or (proliferative (retinopathy	14	13	13	12
MICROVASCULAR COMPLICATIONS AND NEUROPATHY (peripheral and/or (autonomic	26	22	19	20
MICROVASCULAR, MACROVASCULAR AND NEUROPATHIC COMPLICATIONS	26	23	19	21

1:5 INSULIN SPECIES, ANTIBODIES, CONTROL AND COMPLICATIONS

The effect of insulin species on metabolic control and complications was investigated at entry to the study and during the 1st year.

Of the 147 who were initially randomised to blood or urine testing, 81 patients were receiving treatment with bovine insulin, 58 with porcine and 8 with biosynthetic human insulin at entry to the study. 21 patients remained on porcine insulin and 20 on bovine insulin because glycaemic control was judged to the satisfactory on their regime at that time. The remaining 106 patients were randomised to either beef or human insulin the day following admission to the study. 56 individuals (previously on beef (33), porcine (22) or human (1) insulin) were randomised to beef insulin whilst the remaining 50 (previously on beef (29), porcine (14) or human (7) insulin) were randomised to biosynthetic human insulin. I thereafter compared the effects of different insulin species on progress during the 1st year of the study. Of 76 subjects on beef insulin, 36 were randomised to blood testing, whilst 40 carried out urine testing, and overall 61 completed the study. 24 patients treated with human insulin carried out blood testing and 26 urine testing, and 46 completed the 1st year. Of those 21 treated with porcine insulin 8 and 13 were randomised to blood and urine testing respectively, and 17 completed the study.

RESULTS:

GLYCAEMIC CONTROL: Glycaemic control assessed by all variables improved appreciably during the initial phase of the study in

comparison to data at trial entry in patients on bovine or human insulin. Glycaemic control tended to be better at trial entry in the group treated by porcine insulin, so that changes with time in the porcine insulin treated group were less marked. No significant differences in glycaemic control were recorded between the groups at any time point, when assessed by HbA_1 (Table 81), nor by fructosamine or direct measures of glycaemia (data not shown), although HbA_1 levels were a little higher in the bovine insulin treated group and lower in the porcine group,particularly after three months. GSA levels were a little more variable, although they tended to be high in the bovine insulin group, and this difference was significant ($p<0.05$) after 3 months (Table 81).

LIPIDS AND LIPOPROTEINS: Lipid and lipoprotein levels improved overall in the bovine and human insulin treated groups in particular, in comparison to baseline levels. Overall there was no difference between any of the lipid and lipoprotein parameters at any time point between the bovine, porcine or biosynthetic human insulin treated groups (Table 82, Figure 45). HDL cholesterol levels fell after trial entry and remained lower in the porcine insulin treated group during the study ($p<0.05$, Figure 45).

INSULIN ANTIBODIES : A degree of cross-reactivity was observed between human and bovine insulin antibodies and corresponding types of insulin treatment. Both human and bovine insulin antibody titres rose during the year in the group who received bovine insulin ($p<0.01$), whilst in the group treated with human

insulin, a fall was observed in the insulin antibody titres to bovine ($p<0.05$) and to a lesser extent, to human insulin. As expected, the human and bovine antibody titres remained unchanged in the group treated continuously with porcine insulin. (Table 83). Consequently insulin antibody titres to both human and bovine insulin were significantly elevated after 6 weeks, 6 months and 1 year in the patients treated with the more antigenic bovine insulin ($p<0.01$ to 0.001) (Table 83).

COMPLICATIONS : Despite greater insulin antibody titres and suggestively poorer glycaemic control, the prevalence of microvascular, macrovascular and neuropathic complications was similar irrespective of the type of insulin species both an entry to the trial, and after 1 year.

1:6 DISCUSSION

In trying to separate difference features of IDDM, the data presented in this chapter show that both metabolic control and complications in IDDM may be modified by specific influences particular for one individual or group of individuals. In section 1:1 I was able to demonstrate that one complication of IDDM (autonomic neuropathy) may have a bearing on the progress of another (nephropathy). In chapter 4, section 1:2, I described that diabetic microvascular and macrovascular disease may be linked with an increased prevalence of large vessel disease accompanying early diabetic nephropathy. Whilst factors initiating the development of complications may remain unclear, a

Table 81

GLYCAEMIC CONTROL ASSESSED BY HbA_1 (%) AND GSA (%) ACCORDING TO TYPE OF INSULIN SPECIES

	TYPE OF INSULIN SPECIES		
	BOVINE	BIOSYNTHETIC HUMAN	PORCINE
No. of patients			
At trial entry following randomisation	76	50	21
After 1 year	61	46	17
HbA_1 (%)			
Trial entry	9.4 (0.2)***	9.4 (0.2)***	8.9 (0.6)
Randomisation to blood or urine testing	8.2 (0.1)	8.1 (0.2)	8.2 (0.6)
3 months	8.2 (0.2)	7.7 (0.2)	7.8 (0.4)
6 months	8.3 (0.2)	8.2 (0.2)	7.7 (0.4)
9 months	8.3 (0.2)	8.1 (0.3)	8.2 (0.5)
1 year	8.4 (0.2)	8.0 (0.2)	8.1 (0.4)
GSA (%)			
Trial entry	10.4 (0.5)***	10.9 (0.6)***	7.6 (0.8)***
Randomisation to blood or urine testing	8.2 (0.4)	8.3 (0.5)	7.3 (1.0)
3 months	9.8 (0.5)*	7.9 (0.5)	7.7 (0.8)
6 months	8.8 (0.5)	8.3 (0.6)	9.0 (1.1)
9 months	9.1 (0.5)	8.9 (0.6)	8.0 (0.8)
1 year	8.7 (0.5)	8.2 (0.5)	8.2 (1.0)

Figures are mean (SEM)
* $p<0.05$ between groups
***$p< 0.001$ within groups

Table 82

CHANGES IN SERUM TRIGLYCERIDES, HDL CHOLESTEROL SUBFRACTIONS AND APOLIPOPROTEIN B DURING THE HOME BLOOD GLUCOSE MONITORING STUDY IN PATIENTS TREATED WITH BOVINE, PORCINE OR HUMAN INSULIN

	TYPE OF INSULIN SPECIES		
	BOVINE	BIOSYNTHETIC HUMAN	PORCINE
TRIGLYCERIDES (mmol/l)			
Trial entry	*1.29 (0.57-8.15)	1.39 (0.39-3.84)	0.98 (0.57-23.29)
Randomisation to blood or urine testing	1.09 (0.34-4.70)	1.29 (0.24-9.38)	0.98 (0.59-19.39)
6 months	1.24 (0.29-6.44)	1.09 (0.19-4.94)	1.03 (0.29-58.90)
1 year	1.19 (0.29-8.90)	1.11 (0.44-5.89)	1.09 (0.59-11.89)
HDL_2 CHOLESTEROL (mmol/l)			
Trial entry	0.70 (0.04)	0.75 (0.04)	0.76 (0.07)
Randomisation to blood or urine testing	0.73 (0.04)	0.78 (0.06)	0.74 (0.10)
6 months	0.71 (0.04)	0.72 (0.05)	0.75 (0.08)
1 year	0.67 (0.04)	0.75 (0.05)	0.75 (0.08)
HDL_3 CHOLESTEROL (mmol/l)			
Trial entry	** 0.70 (0.03)	* 0.72 (0.03)	0.74 (0.07)
Randomisation to blood or urine testing	0.63 (0.03)	0.66 (0.04)	0.66 (0.09)
6 months	0.69 (0.02)	0.66 (0.03)	0.63 (0.06)
1 year	0.75 (0.03)	0.76 (0.04)	0.67 (0.06)
APOLIPOPROTEIN B (mg/dl)			
Trial entry	101 (3)	102 (4)	98 (5)
Randomisation to blood or urine testing	99 (3)	102 (3)	98 (6)
6 months	100 (3)	107 (4)	101 (5)
1 year	105 (3)	99 (3)	103 (7)

Figures are median (range, mean (SEM)
* $p < 0.05$ ** $p < 0.01$ within groups

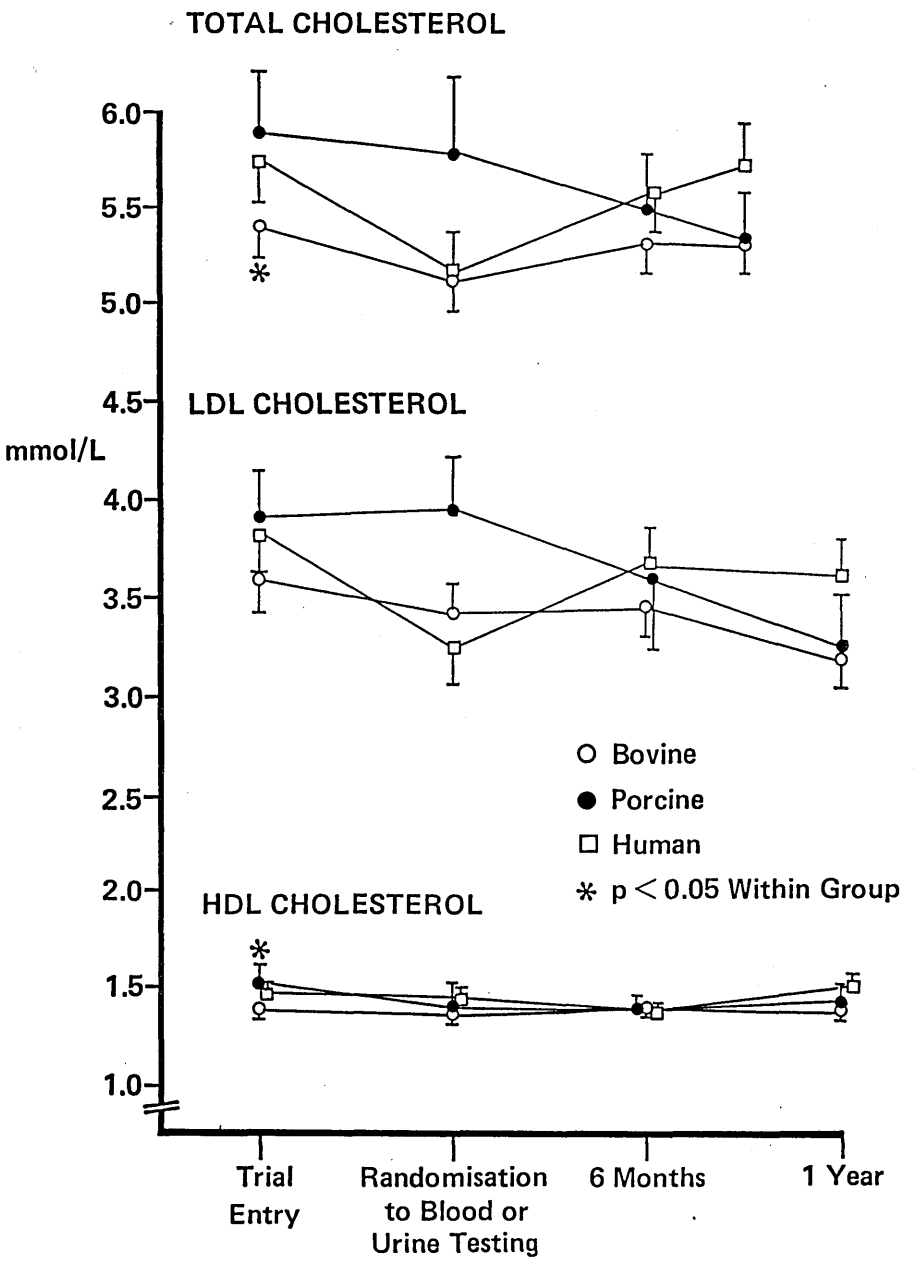


FIG. 45 Total plasma, HDL and LDL cholesterol levels during the home blood glucose monitoring study according to the type of insulin species.

Figures represent Mean ± SEM

Table 83

HUMAN AND BOVINE INSULIN ANTIBODY TITRES DURING THE YEAR IN PATIENTS TREATED WITH BOVINE, PORCINE OR BIOSYNTHETIC HUMAN INSULIN

	TYPE OF INSULIN SPECIES		
	BOVINE	BIOSYNTHETIC HUMAN	PORCINE
BOVINE INSULIN ANTIBODY TITRE (BINDING UNITS)			
Trial entry ***	17.8 (3.1-224.0)	*17.0 (3.6-224.0)	13.8 (4.9-64.0)
Point of randomisation to blood or urine testing	25.0 (6.0-292.0)***	12.5 (3.9-220.0)	14.1 (4.9-51.0)
6 months	23.0 (6.4-196.0)***	12.5 (3.6-216.0)	14.8 (4.1-52.0)
1 year	22.5 (3.1-200.0)**	11.5 (3.1-116.0)	14.6 (6.2-46.0)
HUMAN INSULIN ANTIBODY TITRE (BINDING UNITS)			
Trial entry ***	15.5 (2.7-206.0)	17.2 (2.5-256.0)	13.5 (3.0-62.0)
Point of randomisation to blood or urine testing	25.0 (4.2-232.0)**	13.5 (2.5-228.0)	16.3 (2.6-51.0)
6 months	21.5 (4.9-96.0)**	14.3 (2.5-268.0)	11.3 (3.9-52.0)
1 year	20.3 (2.8-116.0)*	13.1 (2.5-132.0)	15.0 (7.4-43.0)

Figures are median (range)

Differences within groups * $p<0.05$ *** $p<0.001$
Differences between groups * $p<0.05$ ** $p<0.01$ *** $p<0.001$

'cascade of complications' may operate once particular features (i.e. autonomic neuropathy, hypertension, nephropathy) have become established.

The finding of an increased AER in association with autonomic neuropathy, particularly at night (section 1:1), was novel. However it provides one further potential explanation, along with metabolic control and hypertension, why only 50% of patients with IDDM develop nephropathy (360). The likeliest mechanism for this phenomenon would be via the effects of the autonomic nervous system on renal haemodynamics. Renal hyperfiltration is associated with increased AER (650), and may be the consequence of the reduced splanchnic vascular resistance demonstrated in autonomic neuropathy (660). The hyperfiltration hypothesis (623) for the development of diabetic nephropathy may therefore be subject to modification by altered sympathetic vascular tone. Sympathetic renal tubular denervation may provide a further explanation for enhanced urinary protein as well as urinary sodium excretion. The observation that renal handling of protein and sodium was more disturbed in diabetic autonomic neuropathy partly reflects the importance of posture in renal function. Renal blood flow normally increases in healthy subjects whilst supine (740); therefore pre-existing derangements of renal haemodynamics in diabetic nephropathy might be subject to further modification at night, as has been observed previously in non-diabetic autonomic neuropathy (363). This may in turn explain the increased nocturia, natriuresis and AER.

Autonomic neuropathy has also been associated with reduced plasma renin activity (PRA) in diabetes (741,742),

although associated juxtaglomerular sclerosis is more likely to be implicated in the cause (742) than autonomic neuropathy, as infusions of noradrenaline had little effect of PRA in such patients (742). Finally, vasopressin levels may sometime fail to repond to postural stimuli in autonomic neuropathy, contributing to natriuresis and early polyuria on waking (741). Whatever the precise pathophysiology, these abnormalities together will certainly contribute to the exaggerated early morning orthostatic hypotension of diabetic autonomic neuropathy (742).

In sections 1:2-1:4, I examined the metabolic and clinical consequences of persistent C-peptide (i.e. endogenous insulin) secretion.

The overall comparison from the cross-sectional and the longitudinal studies was that residual β cell function does beneficially influence glycaemic control in IDDM. However it is clear that this effect is of relatively minor importance, since cross-sectional comparisons often failed to show significant differences in glycaemic control, and it was often GSA levels rather than the less sensitive glycaemic index or HbA_1, that were different amongst patients with residual C-peptide secretion. In chapter 5, I found that GSA was a more sensitive index of glycaemic instability than HbA_1, and it would appear that the measurement of this more sensitive index may be necessary for future investigations of the role of C-peptide and other potential determinants of glycaemic control. It was also clear from the longitudinal study that the influence of a residual C-peptide reserve on glycaemic control is not an 'all or none' phenomenon. Whilst HbA_1 levels only appeared lower in the high

C-peptide group, a graded reduction in GSA levels was apparent in the negative, low and high C-peptide responder groups at virtually all time points.

In contrast to the effect on glycaemic control, persistant C-peptide secretion seems to bring little influence to bear on lipid and lipoprotein levels in IDDM. In the cross-sectional study, I found that serum triglycerides and differences in gender were the most important determinants of HDL cholesterol in IDDM, whilst C-peptide exerted a minor effect on HDL_2 cholesterol, and no significant predictions of HDL_3 cholesterol were found. No difference in any lipid or lipoprotein estimations were found between the negative low or high C-peptide groups. These findings are in contrast to the only other large study to examine the role of C-peptide on lipoproteins in IDDM (293), where an independent inverse relationship between HDL and HDL_2 cholesterol and C-peptide was observed. However that study by Laakso et al (293) concentrated on middle-aged insulin treated diabetics, and the group with the higher C-peptide levels were markedly hypertriglyceridaemic, and were characterised by poorer glycaemic control, obesity and a higher daily insulin dose, in contrast to the C-peptide responders in my investigation. Despite the use of multivariate analysis to correct for these compounding factors, the high C-peptide group studied by Laakso et al (293), were in effect a group of non-insulin dependent diabetics treated with insulin. On that assessment their lower HDL and HDL_2 cholesterol levels would have been anticipated on the basis of numerous reports (262,743-748), and would not necessarily be the consequence of higher C-peptide levels. I

also found no relationship between HbA_1 and HDL levels in IDDM, and my overriding impression is that HDL levels in IDDM are modified predominantly by the ambient hypertriglyceridaemia, alcohol and tobacco consumption, and exercise, rather than by residual C-peptide secretion or glycaemic control, unless there is profound insulin deficiency, when HDL levels will fall. The cause of the relatively high HDL cholesterol levels in IDDM remains unclear, and apparently unrelated to an alteration in the portal supply of insulin to the liver. Furthermore residual C-peptide secretion bore no influence on lipid and lipoprotein levels during the prospective phase of the study, so as with glycaemic control, it would appear that other factors which influence lipids and lipoproteins in IDDM (e.g. diet, insulin supply, apoprotein polymorphism and renal disease) are more relevant than residual β-cell function. Despite relatively minor changes in glycaemic control and no alteration in lipids and lipoproteins, a consistently reduced daily insulin dosage was achieved in the high C-peptide group during the longitudinal analysis of all 147 patients. In addition to helping minimise weight gain, the effect of reduced peripheral hyperinsulinaemia on the vasculature may be a futher potential advantage. It should be noted in the study of longer standing IDDM (1:4), that the daily insulin dosage was no different between those patients with and without C-peptide secretion, so that any differences in peripheral hyperinsulinaemia would if anything be reversed, with higher levels in those with circulating C-peptide. In this study I also found that glycaemic control tended to be better in patients with C-peptide secretion, particularly when assessed by

GSA. With regard to the prevalence and evolution of complications, I found that the prevalence of proliferative retinopathy was greater, and that of background retinopathy less, in those without detectable circulating C-peptide at inception to the study, in support of the study by Sjoberg et al (557). However the incidence of retinopathy development was such that the prevalence of background and proliferative retinopathy was virtually identical in the two groups after 1 year. This would suggest that time (i.e. duration of disease) is a more important factor for the progression of retinopathy than persistant C-peptide secretion and metabolic control. This fact also helps make the point that whilst persistant circulating C-peptide may lead to marginal improvements in glycaemic control, this effect is not sufficient to have any impact on the natural history of diabetic microvascular disease, particularly since renal function was also virtually identical after 1 year in both groups. I also found that residual β cell function had no bearing on the prevalence or incidence of diabetic neuropathy. This is in keeping with the observations of Sjoberg et al (554) and again suggests that a threshold effect for improvement in neuropathy is not attained simply by the minor effect of residual C-peptide on glycaemic control.

The number of patients with ischaemic heart disease and/or hypertension remained comparable in long standing IDDM with and without circulating C-peptide, but an increased prevalence of peripheral vascular disease was a feature of the group with C-peptide secretion, an observation also shown recently by Ronnemaa et al (749). Ronnemaa et al (749) studied mainly non-insulin

dependent diabetic patients treated with insulin and found the highest prevalence of large vessel disease amongst women, who formed a minority of the patients in my study. Despite these differences, one noteworthy point is that the daily insulin dose was similar in both studies in patients with and without C-peptide secretion, so relative hyperinsulinaemia and/or insulin resistance was probably a feature of those patients with detectable C-peptide. Although it remains uncertain whether hyperinsulinaemia per se or insulin resistance is more important, there is circumstantial evidence from clinical (16, 750, 751) and in vitro (752) studies that insulin may be important for the development of atherosclerosis in insulin-resistant states.

The prevalence of peripheral vascular disease was only significantly greater at entry to the study, but it should be pointed out that were it not for the withdrawal of 1 subject from the study following limb amputation, the prevalence of peripheral vascular disease after 1 year in the C-peptide responsive group would have remained greater.

Like most (555, 643, 753-755), although not all (756, 757) previous reports, I found no relationship between insulin antibodies and either the presence or absence of persistant C-peptide secretion or the loss of B-cell function over 2 years. In addition I could not confirm previous observations of an association between high insulin antibody titres and microvascular complications (372, 373, 617), and found that insulin antibodies had no impact on lipid and lipoprotein levels during the study, although glycaemic control was suggestively poorer in the group treated with bovine insulin, who had the

highest antibody titres. It would appear in practice, that insulin antibodies make little difference to either metabolic control or the development of complications.

Finally the observation of attenuation of the C-peptide response with time merits discussion. 8 patients lost the capacity to produce C-peptide after 1 year, often accompanied by poor metabolic control in relation to those in whom C-peptide secretion persisted. The majority of these (6 of the 8) had low C-peptide levels (<0.060 pmol/ml) at entry to the study, but it was of interest to record that glycaemic control was particulaly poor in the remaining 2 individuals with higher C-peptide levels initially (0.100 and 0.360 pmol/ml). Therefore it would appear that whilst strict metabolic control itself may not necessarily lead to recovery of B-cell function in the long term (551, 758), gradual destruction of the B-cell reserve is a feature of IDDM, and the process may be accelerated by poor glycaemic control, presumably due to'exhaustion' of the Beta cells.

CHAPTER 7

PSYSCHOSOCIAL ASPECTS

All participants in the home blood glucose monitoring study were given the opportunity to complete questionnaires designed to give an index of several psychosocial parameters. The M.H.L.C. (Multi Health Locus of Control) questionnaire was administered to give an assessment of patient's beliefs about health and in particular an idea of the relative importance of the individual, chance or the health care professional in its determination. The Zung rating gave an idea of depressive symptoms, the Epstein Fenz questionnaire assessed the degree of anxiety and gave separate ratings for feelings of insecurity, muscle tension or the physical component due to autonomic arousal. The Leyton inventory assessed the prevalence of obsessional symptoms and traits, which were assessed separately. Finally, IQ was assessed by the Mill Hill questionnaire which gave scores for vocabulary (synonym score) and abilities in solving problems of pattern recognition (standard progressive matrices). The questionnaires were administered on separate occasions during the initial period of the study whilst intensification of management was underway. Patients completed them without assistance from medical or nursing staff, and independent of members of their family or advice from other patients.

The intention of this part of the study was :

1) to assess the prevalence of psychopathology in our study group

2) to determine the relationship between the various aspects of the psyche and metabolic control

3) To investigate whether the presence of or concern for the development of complications or specific beliefs about diabetes affected psychometric evaluation

4) to see whether performance in the home blood glucose monitoring study was related to psychological status.

1:1 PREVALENCE OF PSYCHOPATHOLOGY

Complete psychometric data was available on 130 (83 men and 47 women) of the 147 subjects who were randomised after the initial 6 week period of intensified management. Abnormal scores on psychological tests indicative of psychopathology were based on normal data collected in the Department of Psychology at Hope Hospital by Dr. Chris Mains or from a previous report in the case of the Leyton Inventory (759), and were greater than the upper 95% confidence limits of the diabetic patient population in the current study.

Zung Depression Inventory

A maximum possible score of 60 was attainable with the Zung rating and values greater than 26.9 for women and 23.0 for men were compatible with a clinical diagnosis of depression. 19 (14.6%) of the 130 patients were classified as having an abnormal Zung rating, of whom there were 9 (19.1%) women and 10 (12.0%) men, with a significantly greater prevalence ($p<0.01$) amongst women.

Leyton Obsession Rating

68 questions were asked, with a maximum possible symptom score of 46 and a maximum trait score of 22. Based on data from patients with obsessional neurosis, houseproud housewives and their spouses, and 'normal men and women' (759), abnormal symptom scores of >22.4 for women and >17.8 for men were established,

with abnormal trait scores of >11.4 and >10.9 respectively. Abnormal Leyton symptom scores were recorded in 34 (41.0%) of men but in only 10 (21.3%) of women ($p<0.01$), whilst the prevalence of abnormal trait scores was similar in men (24 (28.9%) cases) and women (16 (34.0%)).

Epstein Fenz Anxiety Ratings

The questionnaire consists of 45 questions and a maximum rating of 5 is theoritically possible for each of the 3 fifteen question components (Autonomic Arousal, Muscle Tension and Feelings of Insecurity). Abnormal autonomic arousal scores of greater than 2.85 for women or 2.40 for men were recorded in 10 (12.0%) men and 4 (8.6%) women, whilst the score was abnormally low (less than the lower 95% confidence limit for all patients) in 2 men and 2 women. A similar prevalence of high muscle tension scores was recorded in 9 (10.8%) men (score >2.10) and in 6 (12.8%) women (score >2.26). The most surprising feature was that very low Feelings of Insecurity ratings were recorded in 18 (38.3%) women and 47 (56.6%) men ($p<0.05$), whilst abnormally high levels (3.36 for men and women) were apparent in 5 (10.6%) women but not in any men.

Associations between Psychometric Tests and Demographic Factors

There was no difference between males and females for IQ, MHLC, Zung or Leyton Scores, nor for the Autonomic Arousal and Muscle Tension components of the Epstein Fenz questionnaires. However the Epstein Fenz Feelings of Insecurity Score was significantly lower ($p<0.05$) in men. Employment status had no bearing on IQ, Leyton, Epstein Fenz Autonomic Arousal and Muscle Tension Scores, or most of the MHLC ratings, but higher Zung

Depression Ratings ($p=0.001$), Epstein Fenz Feelings of Insecurity Scores ($p<0.001$) and MHLC self-help scores ($p<0.001$) were recorded in those patients who were unemployed. Differences in social class had no bearing on Epstein Fenz, Leyton or MHLC ratings, although the IQ symptom ($p<0.05$) and standard progressive matrics ($p<0.01$) scores were lowest, and Zung Depression Ratings highest ($p<0.05$) in Social Class groups IV and V. The duration of diabetes did not correlate with any psychometric score although patient age was positively correlated with Zung and Leyton Scores. In general terms mean Zung depression and Epstein Fenz autonomic arousal and muscle tension ratings were no different to previous studies of healthy controls. The Leyton symptom score in particular was higher than previously recorded in healthy controls, whilst the feeling of insecurity score was lower than anticipated. The Zung depression scores were significantly correlated with the Leyton symptom score ($r=0.40$, $p<0.001$) and the Leyton trait score ($r=0.24$, $p<0.01$). In addition Zung scores correlated closely with Epstein Fenz autonomic arousal ($r=0.42$, $p<0.001$), muscle tension ($r=0.48$, $p<0.001$) and feelings of insecurity ($r=0.62$, $p<0.001$) scores. The Leyton Symptom scores correlated closely with the Epstein Fenz autonomic arousal ($r=0.39$, $p<0.001$), muscle tension ($r=0.41$, $p<0.001$) and feelings of insecurity ($r=0.55$, $p<0.001$) ratings, whilst Leyton trait score correlated with Epstein Fenz autonomic arousal ($r=0.24$, $p<0.01$), muscle tension ($r=0.19$, $p<0.05$) and feelings of insecurity ($r=0.35$, $p<0.001$) to a lesser degree. MHLC scores correlated with one other with the exception of the self-help component. The powerful others component correlated

with the Zung and the Leyton symptom and trait scores (all $p<0.001$), and the Epstein Fenz feelings of insecurity score ($r=0.22$, $p<0.01$). The MHLC chance score correlated with the Epstein Fenz Autonomic Arousal rating ($r=0.26$, $p=0.02$). Of a maximum score of 36 for each of the MHLC sections, the highest score was recorded for the internal/external scale (27.5 (0.4)), followed thereafter by powerful others (23.1(0.6) and chance (17.0(0.6)), and then a particularly notable low self help score (11.8(0.2)). The number of men and women with abnormal psychological scores for more than 1 parameter are shown in Tables 83 and 84. In general, men and women with abnormal Zung depression or Epstein Fenz anxiety ratings had abnormal Leyton symptom and trait scores in roughly 50% of cases. On the other hand abnormal Zung and Epstein Fenz scores were recorded together in 3-4 females but only in 1 male (Tables 84, 85).

TABLE 84

Number of male patients with abnormal psychological scores in more than 1 test (Total number = 83).

Test	Zung	Leyton Symptom	Leyton Trait	Epstein Fenz Ratings: Autonomic Arousal	Epstein Fenz Ratings: Muscle Tension	Epstein Fenz Ratings: Feelings of Insecurity
Total Number with Abnormal Score	10	34	24	10	9	0
Zung	-	5	4	0	1	0
Leyton Symptom	5	-	17	7	7	0
Leyton Trait	4	17	-	7	5	0
Epstein Fenz Autonomic Arousal	0	7	7	-	7	0
Epstein Fenz Muscle Tension	1	7	5	7	-	0
Epstein Fenz Feelings of Insecurity	0	0	0	0	0	-

TABLE 85

Number of Female patients with abnormal psychological scores in more than 1 test (Total number = 47)

Test	Zung	Leyton Symptom	Leyton Trait	Epstein Fenz Ratings: Autonomic Arousal	Epstein Fenz Ratings: Muscle Tension	Epstein Fenz Ratings: Feelings of Insecurity
Total Number with Abnormal Score	9	10	16	4	6	5
Zung	-	4	5	4	3	3
Leyton System	4	-	8	2	2	3
Leyton Trait	5	8	-	2	2	4
Epstein Fenz Autonomic Arousal	4	2	2	-	3	2
Epstein Fenz Muscle Tension	3	2	2	3	-	2
Epstein Fenz Feelings of Insecurity	3	3	4	2	2	-

1.2 PSYCHOMETRIC EVALUATION: RELATION TO GLYCAEMIC CONTROL

Levels of mean blood glucose, GSA, HbA_1, and frequency and knowledge of hypoglycaemic symptoms did not correlate significantly with any psychometric score for the total group. When data on males and females were pooled and psychometric scores compared in the 66 and 64 subjects with respectively lower and higher HbA_1, values than an arbitrary level of 9.1%, a significantly greater proportion with high levels had abnormal Leyton symptom scores ($p<0.03$), whilst abnormal Zung depression scores were suggestively more common ($p=0.08$) in this group. 4 of the 14 subjects who claimed to experience daily hypoglycaemic episodes perhaps unsurprisingly had abnormally high Epstein Fenz autonomic arousal scores, in comparison to 16 of the remaining 116, who allegedly experienced less frequent hypoglycaemia ($p=0.01$). However mean Zung, Leyton and Epstein Fenz scores were not significantly different amongst patients with lower or higher HbA_1 levels, or those with daily or less frequent hypoglycaemia.

1.3. PSYCHOMETRIC EVALUATION: RELATION TO COMPLICATIONS

Impotence: The presence of impotence was unrelated to MHLC, Leyton or Epstein Fenz scores, but was significantly correlated with the Zung depression rating ($r=0.28$, $p<0.01$). Furthermore, more male subjects with impotence had abnormal Zung scores than those without (8 v 2, $p<0.01$). Social class distribution and employment status were no different amongst men with and without impotence.

Retinopathy : The presence of proliferative retinopathy was unrelated to any psychometric evaluation apart from higher Epstein Fenz autonomic arousal scores ($p<0.05$).

Ischaemic Heart Disease : The presence of IHD was unrelated to any psychological trait other than the Zung Depression score, when scores were significantly greater (17.3(2.3) v 13.0(0.7) (mean (SEM), $p=0.02$). However more patients with abnormal Leyton symptom and trait scores had ischaemic heart disease than those without high scores ($p<0.05$) and IHD was also more common in those subjects who were unemployed ($p<0.05$).

Peripheral Vascular Disease: Patients with peripheral vascular disease had a higher Zung depression rating that those without (16.1(2.4) V 13.1(0.7), $p<0.05$), but no other association with psychological parameters was recorded, other than abnormal Epstein Fenz muscle tension scores, which were recorded more frequently in patients with peripheral vascular disease ($p=0.02$), who were more commonly unemployed ($p<0.01$).

Peripheral Neuropathy: Neuropathic symptoms were more conspicuously associated with depression and anxiety than signs of neuropathy or with other complications. There were more patients with low neuropathy scores (24) than with neuropathic symptoms (13). As well as a significant association between the Zung depression rating and the extent of neuropathic symptoms ($r=0.26$, $p<0.001$), patients with sensory neuropathic symptoms had a higher Zung rating than those without (19.7(2.6) V 12.8(0.6), $p<0.01$). Furthermore abnormal Zung ratings were more commonly observed in those with sensory neuropathy symptoms ($p<0.05$). A low clinical neuropathy score (in more extensive neuropathy) was inversely related to the Zung score ($r=-0.27$, $p=0.005$), but low neuropathy scores (<11) were not significantly more prevalent amongst patients with abnormal Zung scores. Neuropathic

symptoms were also associated with the Epstein Fenz autonomic arousal ($r=0.26$, $p<0.001$) and muscle tension ($r=0.38$, $p<0.001$) scores. The autonomic arousal score was greater in patients with symptoms of neuropathy(2.19(0.13) V 1.85(0.04), $p=0.01$), and were frequently abnormal in these patients ($p=0.001$). Likewise the muscle tension score was greater in patients with symptoms (1.99(0.16) V 1.46(0.04), $p<0.005$), in whom it was more frequently abnormally high ($p<0.001$). Interestingly the neuropathy score was not related to Epstein Fenz anxiety ratings. There was no relationship between clinical features of neuropathy and the Epstein Fenz feelings of insecurity score, or the MHLC or Leyton scores.

1:4. ROLE OF PSYCHE DURING HOME BLOOD GLUCOSE MONITORING PROJECT

Patient Compliance and Psychological Status: Patients were asked at entry to the study whether or not they always carried a source of carbohydrate and/or diabetic identification with them, in keeping with the suggestion by Lockington et al (527), that this assessment gave a reasonable indication of patient compliance with their self-care programme.

70% of patients regularly carried both diabetic identification and a source of carbohydrate, whilst only 4% carried neither. The Zung depression, Leyton obsession and Epstein Fenz anxiety ratings were no different amongst those subjects who did or did not carry carbohydrate or diabetic identification.

Following randomisation to blood or urine glucose testing, compliance in the study was assessed from the number of completed

filter card blood spots suitable for analysis over the ensuing twelve month period. The number of blood spots per patient ranged from 29 to the maximum of 120. Regardless of gender, patients who submitted 70 or less spots (20% of cases) did not differ from the remaining 80% with regard to their initial psychological status when assessed by Zung, Leyton, Epstein Fenz or MHLC ratings. Furthermore those who submitted 70 or less blood spots (deemed non-compliers) were no different from the remaining group with regard to social class, employment status, or glycaemic control when assessed by three monthly glycosylated blood protein measurements.

Relation of psyche to contact patterns during the home blood glucose monitoring study: Following randomisation, those 19 patients with abnormal Zung depression ratings made significantly more contacts with their GP (0.67(0.29) V 0.25(0.08) contacts per patient (mean (SEM)), $p=0.01$) and myself (0.44(0.24) V 0.13(0.05) contacts per patient, $p<0.02$) over the first three months. Although the group with higher Zung ratings also spent significantly more days off work during the year (36.6(23.8) V 7.1(1.6) days per patient, $p<0.05$), this probably reflected the higher prevalence of complications.

Abnormal Leyton symptom scores were not associated with more frequent contacts, but those 9 subjects with an abnormal Leyton trait score contacted the diabetic liaison sister more frequently over the first three months (0.24(0.11) V 0.11(0.08) contacts per patient per month, $p<0.02$), but not thereafter, although the total number of hospital contacts made during the year was also

greater in these patients (2.1(0.4) V 1.3(0.3) contacts per patient per month, $p<0.05$).

Only 4 patients had high Epstein Fenz autonomic arousal ratings, but they made appreciably more contact with the diabetic liaison sister during the first three months (0.42(0.19) V 0.12(0.07) contacts per patient per month, $p=0.0004$). Abnormal Epstein Fenz muscle tension ratings had no bearing on the pattern of hospital contacts, whilst those with notably low Epstein Fenz feelings of insecurity ratings made significantly fewer contacts with the diabetic liaison sister during the first three months (0 V 0.26(0.12) contacts per patient per month, $p<0.005$).

Psychological traits were not associated with other patterns of contact with health professionals, and most notably had no association with contact patterns beyond the first three month period after randomisation.

Changes in Psyche during the home blood glucose monitoring study: 39 of the 124 subjects who completed the first year of the study filled in psychological questionnaires at the one year follow up visit. A notable correlation between the various psychometric measures was observed after one year and importantly there were no significant correlations between changes in measures of glycaemia and changes in psychological status. Overall, mean scores for the Zung, Leyton and Epstein Fenz questionnaires did not differ significantly after one year. The most apparent change was in the MHLC self-help score which rose from 12.0(0.4) to 18.4(0.7), $p<0.001$.

1:5. DISCUSSION

The extent of psychopathology amongst the diabetic population studied was not distinct from previous studies and no greater than the general population with the notable exception of high Leyton obsessional ratings. More important is of course to consider the implications of the adverse psychological status for the management of such individuals. As in the non-diabetic population, I found that the prevalence of high Zung depression scores was higher in women, although an unexpected excess of abnormal Leyton obsessional symptom scores was recorded in men.

The enforced disciplines of self-management of IDDM might be expected to lead to a degree of rigidity in behaviour, reflected in the high Leyton obsession ratings, and the preponderance of men in the population I studied may in part explain the result. Furthermore a considerable difference in upper limits of male and female Leyton symptom scores was less apparent for the Leyton trait scores where the prevalence of abnormal scores was similar in men and women. It would therefore seem that IDDM leads to behavioural changes which reverse the tendency for women to display obsessive symptoms more often than men.

One interesting finding was that, as in the study of Bradley et al (523), I found that the diabetic patients rated the internal/external and powerful others components of the locus of health control highly. In addition a notably low score for the Epstein Fenz feelings of insecurity rating was apparent. Despite this a low self-help locus of health control was recorded. This might suggest that whilst diabetic patients may perceive both positive and negative health outcomes as primarily

attributable to their medical practitioners as well as themselves, so that consequently they were not necessarily insecure, there would appear to be a poor insight into their own ability to beneficially modify patterns of health. It could be argued whether this state of relative security despite a lack of initiative for self-help may in fact be the major obstacle facing health professionals trying to improve diabetic management.

Whilst there does not seem to be an excess of psychiatric illness in IDDM,I found that the burden of psychopathology was heaviest in particular groups of patients, namely those who were unemployed, of lower social class, or the victims of diabetic complications (v.i). It is not possible in the present project to conclude whether unemployment is the cause of the higher depression and feelings of insecurity ratings, but it was of interest to record higher MHLC self help ratings in those who were unemployed, suggesting that despite more mood disturbance, independent behaviour may be the one beneficial accompaniment of unemployment. Perhaps suprisingly, I only found Zung depression ratings were higher in the lower social class groupings. Although all forms of neurotic illness are generally recognised more frequently in lower social classes, the unintentional bias towards selection of most patients from the lower social classes may have led to an excess of anxiety in the current study.

A clear relationship was recorded between patterns of depression and anxiety ratings, and between obsession and anxiety scores. Consequently patients with abnormal Zung depression or Epstein Fenz anxiety ratings often also had high Leyton obsession

scores. Notwithstanding the fact that patients with features compatible with both anxiety and depression were observed less consistently, there would appear to be a group of individuals in whom several neurotic traits are evident, and in whom presumably psychological dysfunction is more extensive and difficult to treat.

Unlike the report from Cassileth et al (540), I did not record more anxiety or depression in patients with a short duration of diabetes, although older patients had higher Zung depression and Leyton obsession scores. The latter finding may simply reflect the luxury of a more ordered existence that growing older provides. One possible explanation for the higher depression ratings in my study may be the presence of more complications in the older patient, which had a major bearing on the psyche (v.i.). The effect of complications may have 'swamped' any apprehension, anxiety or depression that accompanies the diagnosis of diabetes, and in the event relatively few patients in the present study were newly diagnosed. Furthermore it is not stated how many of the diabetic patients of Cassileth et al (540) had complications. It is of interest to note that none of the other chronic diseases that Cassileth et al studied, with possible exception of cancer, usually lead to a physical loss. Loss of vision, limbs (and perhaps potency) were those fears most often voiced by my patients (in Chapter 3), and it was those patients with retinopathy, lower limb neuropathy, and impotence who often had the highest depression and anxiety ratings.

One notable feature was the lack of a consistent association

between metabolic control and psychological factors in patients I studied. More recent reports in IDDM have suggested that anxiety and depression ratings may be higher in poorly controlled subjects (541, 760). Whether hyperglycaemia itself affects mood or disturbed mood affects behaviour and compliance indirectly leading to hyperglycaemia was uncertain. The reason for the discrepancy between the findings are unclear, although patient selection differed with regard to the type of diabetes and/or the presence of complications. Furthermore I was able to demonstrate that the less compliant patients did have poorer glycaemic control during the study, so it is feasible that whilst these subjects need not necessarily be anxious or depressed, it is their behaviour which led to the poor glycaemic control in the reports by Mazze et al (541) and Robinson et al (760). My observation that high anxiety ratings were recorded more frequently in patients with frequent hypoglycaemia confirms the findings of Sanders et al (539), and in practice the relationship between mood and recurrent hypoglycaemia is perhaps more relevant than that with hyperglycaemia, where compliance is the real issue. Finally the limitations of questionnaires in evaluating mood and stress should be acknowledged. The type of acute anxiety and stress that may lead to hyperglycaemia (533, 543) may not always be reflected by a high Epstein Fenz rating.

I found that the presence of complications, particularly neuropathy and retinopathy, was the most consistent predictor of psychological disturbance. It is now becoming clearer that the specific complications where the loss of vision or limbs is perceived as a threat by the patient are most clearly associated

with altered mood and increased anxiety, and my observations are in keeping with several other previous reports (537, 538, 546, 547, 760). The association between coronary heart disease and a higher depression rating in diabetics confirms previous findings in non-diabetics (544).

Finally, the higher depression rating in impotent men supports recent work (547) and it is perhaps not suprising that 'loss of manhood' is another 'potent' mood depressing stimulus.

In summary it would appear that psychological disturbances are not particularly common in IDDM, with the exception of obessional traits, which may be encouraged by the process of diabetic self-management. Glycaemic control is not strongly associated with psychological status in general, other than in maladapted non-compliant individuals. The most striking observation is that diabetic patients with complications carry a heavy psychological load, particularly if there is evidence of serious retinopathy, neuropathy or impotence. The co-existence of neuropathy and depression in particular may be of practical importance since psychological disturbances can often compound neurological disease and indeed atypical dysaesthesiae is a not infrequent manifestation of depression. Therefore the relationship between complications and mood change is a complex one, and not necessarily cause and effect. At any rate there would appear to be evidence to support the need to enquire about psychological disturbance in those subjects with established complications.

Initial psychological status had little bearing on performance during the home blood glucose monitoring study. In

particular, those patients with high anxiety, depression, or obsession ratings did not comply with the study requirements any differently from the remaining group, nor did they experience poorer glycaemic control. However those patients with higher Zung, Leyton and Epstein Fenz ratings did make more demands on health care professionals, but only during the first three months of the study following randomisation. It would therefore appear that this type of intensified management programme might lead to increased patient contact in the short term with subjects who have neurotic tendencies, although this phenomenon will dissipate with time. In view of the relatively small numbers, it is not possible to state whether contact with a particular health care professional (e.g. general practitioner as opposed to diabetic sister) was of any relevance.

Mazze et al (541), previously suggested that improved diabetic management led to improved depression and anxiety ratings, which I could not confirm after one year in the current series of investigations. Comparison of the two studies is rather difficult since it would appear that none of the selected population studied by Mazze et al initially had anxiety or depression ratings high enough to represent psychopathology, so it is debatable whether improved glycaemic control directly improved mood. Whilst my data would suggest that programmes of intensified diabetic self-management do not necessarily modify anxiety, depression or obsessional tendencies, I was able to demonstrate a benefit in patients' perceptions of their health. A definite improved MHLC self-help rating would suggest that diabetic patients' attitudes to illness are more positive

following such a programme and it could be hoped that there might be longer term pay-offs as a consequence of a more independent approach to diabetic management.

CHAPTER 8

GENERAL DISCUSSION AND CONCLUSIONS

The work presented in this thesis throws some light on the broad areas of enquiry that were raised in the introduction.

1. WHAT FACTORS DETERMINE METABOLIC CONTROL?

The first major point to make is that measures of lipid and carbohydrate metabolism in IDDM often give quite distinct information regarding metabolic control, and it is therefore best to discuss these two broad areas separately.

Glycaemic control was assessed by established methods in addition to monthly filter card blood glucose profiles and GSA using affinity chromatography, with methods that I helped to develop as part of the work for the thesis. In addition the clinical performance of the 'fructosamine' assay was subjected to careful scrutiny.

When I examined those factors that improved glycaemic control, I was initially able to analyse the effects of intensive management, and thereafter to assess how important home blood glucose monitoring was, and whether glycaemic control was modified by residual endogenous insulin secretion, insulin species and antibody titre and psychosocial and educational factors.

The most marked improvement in glycaemic control was apparent following the initial 6 week period of intensified management when insulin regimes were modified, patients instructed in diabetic self-management and in blood glucose monitoring, and fortnightly contact and continued education carried out. Improvements in glycaemic control and educational scores were maintained for 1 year.

It is therefore possible to conclude that the initial intensive programme can be applied successfully to large numbers of sub-optimally controlled insulin-dependent diabetics who attend the regular diabetic clinic and whose initial short term improvements can be maintained to a greater or lesser extent for a period of at least 1 year.

The question as to whether it was alteration of the insulin regimen, regular access to medical staff, blood glucose monitoring, or the educational programme that contributed most to the improvement cannot be measured from my study, and it is perhaps unnecessary to attempt to answer it, since the isolation of one particular approach, apart from being difficult in practice, would not be appropriate for good diabetic management. However the easy access policy that was maintained throughout the study may have enabled the group as a whole to maintain their improved glycaemic control, as may have the fact that the improved educational ratings were retained after 1 year in the study.

Before discussing how important other factors were in determining glycaemic control, it is worth considering the different measures of glycaemic control that were made in the various studies.

Firstly, it is important to evaluate the methodological limitations and performance of the various assays. The filter paper blood glucose assay was developed to provide a validated record of direct glycaemic measures for comparison with the glycosylated blood proteins, in addition to a quality control check on patient-generated domestic blood glucose recordings.

The continuous flow auto-analyser system was found to be accurate, sensitive and reproducible, in agreement with previous reports (492-499). The main practical consideration was optimisation of storage conditions. I found that refrigeration of the filter cards without preservative was sufficient to ensure blood glucose stability for up to 28 days, supporting the findings of Seiter et al (492) but contesting those of Burrin et al (495) who found that blood glucose levels fell by as much as 30% after 5 days refrigeration without preservative. I also found that application of boric acid as a preservative led to initial artefactual rises in blood glucose. The reason for this is unclear, but in view of the protective effect of refrigeration, the expense of impregnation of filter cards with preservative, and the failure of others to find that boric acid was an effective preservative (492, 493), I continued to use filter cards without preservative for use by patients during the study.

Although it is impossible to be certain that all patients always refrigerated their filter cads as requested, it is notable that only small falls in filter card blood glucose levels were apparent when stored at room temperature for 48 hours, and previous studies suggested that samples were reasonably stable for up to 1 week under these storage conditions (462, 492, 496). On balance the method produced patient generated results suitable for analysis. Using this approach I was able to confirm as in previous laboratory based studies (476, 477), that the Reflolux blood glucose meter consistently over-read blood glucose recordings in patients' hands, particularly in the low normal to

hypoglycaemic range. This latter finding is of particular importance when one notes how frequently asymptomatic biochemical hypoglycaemia was observed during the study.

The GSA affinity chromatography assay was developed in two stages and ultimately yielded a method that was simple, sensitive and precise. In the initial experiments I was able to confirm previous reports (163, 173) that overloading the columns with protein (in serum) leads to artificially low yields of glycosylated protein. I was also able to confirm that dye binding techniques are unsuitable to measure the small amounts of albumin that are necessary to prevent column overloading (163, 176). The modified method employed immunoturbidimetry which was much more reliable in this respect, and also ensured that recovery of albumin from the column was complete. The between batch precision of the GSA assay was 4-7%, which compared favourably with 1-3% for the fructosamine and 3-6% for the HbA_1 assays. Several previous reports on GSA (120, 168, 171, 172, 177, 178) used bromocresol green to measure albumin in the glycosylated and non-glycosylated fractions, which limit conclusions being drawn from them.

In evaluating the fructosamine kit I found that whilst the method was certainly economical in time and cost, values in hypertriglyceridaemic diabetic patients seemed inappropriately lower throughout the study. Whilst the exact mechanism of the 'fructosamine' reaction remains uncertain, it is difficult to explain this phenomenon fully, particularly as non-diabetic hypertriglyceridaemic sera may apparently produce high fructosamine values (761). One explanation may be that

superoxide generation from glycosylated protein bonds may be relevant to the mechanism of NBT reduction in the fructosamine reaction (213), and it has recently been shown that all lipaemic sera has the capacity to generate free radicals (762). It would appear reasonable to speculate that non-diabetic lipaemic sera might accelerate NBT reduction early in the time course of the reaction leading to higher fructosamine values, whilst in diabetic patients the effect would be to reduce the amount of substrate (NBT) available for reduction by glycosylated serum proteins, leading to relatively low fructosamine values.

Secondly, the results in Chapter 5 make it clear that different measures of glycaemia give information that is complementary, and not always comparable. The most important findings were that GSA and fructosamine respond more than HbA_1 to improved glycaemic control, and that fructosamine and GSA do not necessarily always provide the same information about glycaemic control in IDDM. These observations reflect the inherent instability of IDDM, and suggest that at least 2 different glycosylated blood proteins should be measured to enable an assessment of both short-term and longer-term integrated glycaemia. In a report by Ziel and Davidson (178) it was suggested that GSA and HbA_1 gave broadly interchangeable information about glycaemic control in stable IDDM. I have shown that this is clearly not the case and that seriously discordant information is produced on up to 19% of occasions in patients studied over the course of 1 year. The methodological difficulties in the measurement of GSA were not addressed by Ziel and Davidson (178), which might explain the discrepancy, and to

date, no other studies have evaluated the utility of the different glycaemic measures in clinical practice. With regard to the comparison of the GSA and fructosamine assays, I found that GSA was more sensitive in reflecting shorter term improvements in glycaemic control, as well as correlating better with the M value, an index of glycaemic instability. The serious discordance between GSA and fructosamine recorded on 6-15% of occasions during the year should make it clear that the reduction of NBT in the fructosamine reaction cannot be the only source of the colorimetric change. Regardless of the methodological considerations, GSA and fructosamine levels do not always parallel one another in IDDM. Although the economic argument should not necessarily prevail, it is important to acknowledge that the automated fructosamine assay can be costed in terms of pence, whilst the combined affinity chromatography/immunoturbidimetric GSA assay costs about £1 per sample. On balance it would appear that HbA_1 and either fructosamine or GSA should be routinely measured in the management of IDDM and in future studies of the determinants of glycaemic control and its relationship to vascular complications, in order to give an adequate impression of the short and long-term glycaemia. At present the majority of diabetic clinics and ongoing prospective clinical studies investigating the links between glycaemic control and complications are not using more than one glycaemic measure. It might be argued that since the evolution of vascular complications is a lengthy process, the assessment of longer term glycaemic control by serial measurements of HbA_1 alone would suffice. I would contest

this assertion for several reasons. Firstly, since a particular HbA_1 level may reflect a range of mean blood glucose levels differing by as much as 5mmol/l (140), one could not assume the same degree of glycaemic control for a group of patients with similar HbA_1 levels. Secondly, failure to remove the labile fraction of HbA_1 prior to its measurement is still common practice in hospital laboratories because the procedure is time consuming, and the HbA_1 results may be at least 1.5% higher if there is acute hyperglycaemia at the time of blood sampling which would then misleadingly represent longer term integrated glycaemic control. Finally it is unclear how accurately HbA_1 reflects glycaemic instability, particularly hypoglycaemia, in IDDM.

The use of several measures of glycaemia providing complementary information also proved to be important when evaluating factors which might determine blood glucose control. Following the intensive period of management, those patients with detectable C-peptide levels had better glycaemic control when assessed by HbA_1 and GSA, with a suggestion that even low levels of C-peptide conferred the potential for glycaemic control, although of a relative subtle nature, evident only by differences in GSA levels. It was interesting to record that the differences in fructoasmine levels in the different C-peptide groups following the period of intensive management were much more variable, again suggesting that the fructosamine assay probably measures something in addition to GSA.

The findings that persistent C-peptide secretion did confer the potential for subtle improvements in glycaemic control sits

favourably with the other published work on the subject (551, 554-447) where smaller numbers, and different methods of patient selection and assessment of glycaemic control may have contributed to the lack of a clear consensus.

However other factors had less impact on glycaemic control. The continued use of home blood glucose monitoring beyond the initial period of intensified management was associated with improved glycaemic control in comparison to those who reverted to urine glucose monitoring. The most important feature of this improvement was that it was not overwhelming or apparent for all glycaemic measures at all time points. Direct measures of glycaemia from filter card profiles were most consistently improved, whilst significantly higher GSA levels at 3 months, HbA_1 at 6 months and fructosamine at 9 months were observed in the blood testing group. When put into the context of the previous report by Worth et al (77), it is fair to conclude that long-term blood glucose monitoring does lead to improved glycaemic control but that assessment of HbA_1 levels alone are not sensitive enough to detect this and monthly 24h blood glucose profiles may show the benefit most clearly. I would acknowledge that my study design only allowed me to examine whether continued blood glucose monitoring led to <u>maintained</u> improvements in glycaemic control since the majority had attained good glycaemic control following the initial 6 week period. Nonetheless, other benefits of blood glucose monitoring were apparent apart from the differences in glycaemic control; notably more retention of educational skills, an increase in the MHLC self-help rating, and less absenteeism from work (v.i.). This would suggest that home

blood glucose monitoring not only has a definite role as an educational tool but that it may modify individual's perceptions about how they can manage their own condition. This was achieved without any excess of reported hypoglycaemia, although the increased number of hospital contacts in the blood glucose monitoring group suggests that a back up service is essential, but this degree of reliance on the hospital may be a price worth paying. A similar benefit from such an approach has also been previously reported by Berger and colleagues in Dusseldorf (724, 725, 730), and it is noteworthy in both the Salford and Dusseldorf studies that the opportunity for active self-management led to more frequent use of soluble insulin and a sustained increase in body weight irrespective of the means of glucose monitoring.

The effect of different insulin species and antigenicity on glycaemic control was less apparent, but it appeared suggestively poorer in patients treated with bovine insulin when GSA was used to assess glycaemic control. Presumably this reflects the effect of the higher insulin antibody titre which was the consequence of using a more antigenic insulin. In addition the faster onset of insulin action described with biosynthetic human insulin (381) may be relevant. It is fair to conclude that even if bovine insulin leads to a smoother peripheral insulinaemic profile (374, 375), it does not improve metabolic control.

Finally, I found that psychological factors apparently had very little impact on glycaemic control. The relationship between the psyche and glycaemic control is complex. Although previous reports have suggested that glycaemic control was

related to anxiety and depression (541, 542), it is not clear how this relationship operates other than by an indirect effect of mood on compliance and thereby glycaemic control. These reports were on selected young diabetics free of complications and my own observations that only frequent hypoglycaemia was a feature of patients with abnormal anxiety ratings suggest that glycaemic control may be related to the psyche in a small number of cases.

In contrast to glycaemic control, I found that the disordered lipid metabolism of IDDM was not simply the consequence of adverse diabetic management or impaired metabolic control. In keeping with previous reports (50-54), I found that intensified therapy led to significant reductions in serum levels of triglycerides and total and LDL cholesterol in the short-term. Moreover I was able to demonstrate that these improvements were maintained for the group as a whole for at least 1 year. The reason for such changes are likely to be in the main the consequence of improved insulin delivery and better matching of the insulin dose to the dietary lipid load. It is uncertain whether additional dietary modification had any significant role. However, previous reports have shown that low fat diets are poorly tolerated by insulin dependent diabetic patients at home, particularly in the long run (319, 324) and a notable increase in BMI was observed in the patients I studied, so I think that modified dietary fat intake is not the major explanation for the sustained reduction in total lipids.

I found that HDL_3 cholesterol levels fell after the initial period of improved control, and remained low, whilst HDL_2 levels remained stable, and total HDL cholesterol levels did not alter

appreciably. Other (47, 51, 52) studies have found that the improved glycaemic control is associated with a rise in HDL cholesterol, but have not specified in which of the HDL fractions this took place. One reason for the discrepant findings may be that the degree of insulin deficiency and hyperglycaemia in the previous reports was more severe than in my studies. Consequently HDL levels were initially much lower than I found, and therefore more amenable to correction with insulin repletion.

It is in fact quite reasonable to anticipate that HDL_3 cholesterol levels might have fallen with improved glycaemic control. Glycosylation of the apoproteins of HDL has been shown to lead to enhanced HDL synthesis as well as an increased catabolic rate (181). As HDL_3 is the precursor of HDL_2 following its conversion from nascent HDL, the effect of reducing hyperglycaemia on glycosylated HDL would be expected to be a reduced HDL_3 synthesis.

The effects of improved glycaemic control on apolipoprotein B levels are also unclear. Previous reports have suggested that they rise (47, 54), although in both prevailing glycaemic control was particularly poor at the inception of the study. Whilst I found that apo B levels did not alter significantly in the group as a whole, a dramatic reduction was apparent in the sub-group with combined hyperlipidaemia, who importantly had particularly poor control. Scrutiny of other changes in patients sub-divided according to their initial lipid status was of some interest. Patients with either hypercholesterolaemia or hypertriglyceridaemia in particular seemed more amenable to

correction to normolipidaemia than the combined hyperlipidaemic group. Nonetheless, the improved metabolic state led to definite reductions in all cholesterol fractions in the combined hyperlipidaemic group, including HDL_2 cholesterol, suggesting that a generalised reduction in lipoprotein synthesis took place.

Therefore it would appear that limited improvements in lipid metabolism accompany better glycaemic control, particularly in those subjects who have type IIa or IV hyperlipidaemia using the Fredrickson classification.

The stable insulin dependent diabetic would still appear to have subtle conformational changes in lipoproteins. An enhanced cholesterol: triglyceride ratio in VLDL has been reported in well controlled IDDM (259) and the presence of IDL has been suggested (269) although not confirmed. I was able to demonstrate that the density of LDL in IDDM may be altered due to a saturation of the molecule with cholesterol relative to apoB, and Schonfeld et al have made similar observations (54, 56). All these findings suggest the remnant-triglyceride rich 'LDL-like' particles may accumulate in IDDM regardless of glycaemic control. Despite such changes, I was able to demonstrate that the Friedwald formula is still appropriate to calculate LDL cholesterol in IDDM, which may imply that the build up of IDL (LDL_1) in IDDM will compensate for any saturation of VLDL with cholesterol.

In addition to these changes in VLDL and LDL, I found that alterations in HDL are also an integral part of IDDM. Like most other reports (287, 288, 292-296), I found that HDL cholesterol levels in stable IDDM tend to be higher, and that this mainly reflects the build up of HDL_3 cholesterol (299, 300). I did not

find any significant relationship between HDL and either HbA_1 or C-peptide. A lack of association between HbA_1 and HDL is the conclusion of the majority of previous reports (262, 283, 290, 292, 293, 295, 296), whilst higher C-peptide levels had previously been suggested to be independently associated with reduced HDL and HDL_2 cholesterol levels (293). Patient selection may be crucial in this regard. As stated previously low HDL levels may correlate with high HbA_1 if glycaemic control is particularly poor, and a close inverse relationship between HDL and serum triglycerides may have been important in explaining the aforementioned link with C-peptide, since many patients in the report by Laakso et al (293) with higher C-peptide levels were obese, hypertriglyceridaemic type II diabetics who would of course have been expected to have low HDL cholesterol levels.

These abnormalities of lipoprotein structure may be in part under genetic control. I found a much higher than expected prevalence of $ApoE_2$ homozygosity and noted that as in health, the E2 allele is associated with higher triglyceride and lower cholesterol levels than the E4 allele. This difference in lipid levels reflects altered apoE receptor affinity for the different apoprotein E phenotypes, and would provide a further mechanism by which triglyceride-rich lipoproteins could accumulate in IDDM patients who were $\epsilon 2$ homozygotes. Although C-peptide secretion seemed to be unrelated overall to total, LDL or HDL lipid levels, a portal insulin supply may encourage uptake of IDL in IDDM associated with Apo E_2 homozygosity, since hypertriglyceridaemia was present in only 2 of the 8 subjects whom I found to be E_2 homozygotes.

The influence of renal dysfunction on lipoprotein metabolism in IDDM was more evident. I was able to confirm previous reports (329-331) that mild proteinuria is accompanied by a build-up of atherogenic lipids and lipoproteins and a reduction of HDL and HDL_2 cholesterol in the absence of nephrotic syndrome, but also found that minor renal dysfunction made a significant contribution to lipid levels in IDDM. Urinary loss of HDL_3 may be important in explaining the reduction in HDL cholesterol, particularly if an increased hepatic synthetic rate of nascent HDL could be demonstrated, and the explanation for the increased total and LDL cholesterol levels may also reflect the hepatic response to proteinuria. Whatever the cause, it is evident that lipid metabolism may be significantly altered by early diabetic nephropathy. I was not able to demonstrate a role for tobacco, alcohol consumption or exercise in lipid metabolism in IDDM, although these factors are undoubtedly important. However I did find that women have higher HDL levels than men with IDDM, supporting the findings of Walden et al (343), although they pointed out that the difference between IDDM and healthy controls was attenuated in women compared to men. Finally I found that body mass index has a bearing on lipid levels in IDDM, a feature previously reported by Nikkila and Hormila (292).

In conclusion, it would appear that lipid metabolism in IDDM is more complex than carbohydrate metabolism, and that there appear to be intrinsic abnormalities which may be modified not only by inappropriate diabetic care, but also by changes in renal function and body mass.

2. WHAT ARE THE DETERMINANTS AND ACCOMPANIMENTS OF DIABETIC COMPLICATIONS?

Macrovascular Disease: The aetiology and clinical course of coronary and peripheral vascular disease are often presumed to be the same, although this is not necessarily the case, particularly in diabetes. Despite this, I was able to demonstrate that both types of large vessel disease were associated with an increase in systolic and diastolic blood pressure levels, and it was notable that almost all patients with clinical evidence of atherosclerosis in the current study had diabetic renal disease, since epidemiological evidence clearly shows the vast excess of mortality from atherosclerosis in IDDM to reside in this particular sub-population (560). Borch-Johnsen et al (560), has suggested that the presence of proteinuria operates independently of the traditional risk factors for vascular disease (hypertension, hyperlipidaemia, and smoking), despite the evidence from the present work and many other sources (7-9, 329, 331, 584, 606, 611, 628) that these risk factors are particularly associated with diabetic nephropathy. Regardless of the exact mechanism, it is clear that the development of nephropathy leads to a change in the natural history of diabetic large vessel disease. In this regard, the influence of proteinuria in IDDM on lipid metabolism is of special interest. I found that hyperlipidaemia was uncommon amongst subjects with stable metabolic control and no nephropathy, although conformational changes of LDL and HDL appeared intrinsic to IDDM. These findings provide the basis for further research to investigate the mechanism and consequences of such changes, but do not in

themselves suggest that insulin-dependent diabetics are especially vulnerable to premature atherosclerosis by virtue of their lipid profile.

However, like Eckel et al (329), and Vannini et al (331), I found that proteinuria without renal failure was associated not only with the build up of serum cholesterol and triglyceride levels, but also with a reduction in HDL_2 cholesterol. In addition proteinuria may have led to further conformational changes in lipoproteins, so that overall the patient with diabetic nephropathy could be classified as at risk for macrovascular disease on the basis of associated hypertension and hyperlipidaemia. I was unable to examine the relevance of hyperglycaemia and genetic factors to large vessel disease, but the recorded excess of $apoE_2$ homozygosity raises the possibility of an inherited predisposition to hypertriglyceridaemia and diabetes, and there is support for the suggestion that glycosylation may modify both lipoprotein metabolism and arterial function (597, 600).

Finally, I found an increased prevalence of peripheral vascular disease in subjects with long standing IDDM and residual C-peptide secretion. This may be no more than circumstantial, but is compatable with the concept (16, 749) that peripheral hyperinsulinaemia may facilitate atherogenesis.

Irrespective of the pathophysiology, I found that macrovascular disease was accompanied by unemployment and adverse psychological ratings, particularly the Zung depression scale, and perhaps also certain facets of anxiety and obsessional behaviour. Although depression is often the consequence of

myocardial infarction (544), this aspect of diabetic care may have been neglected in the past and certainly merits further investigation. It was particularly interesting to record a low level of concern regarding vulnerability to heart disease in IDDM, confirming the findings of Bradley et al (523). This possibly reflects a lack of awareness of the importance of atherosclerosis to IDDM which perhaps should be incorporated into further educational strategies, particularly as the epidemic of coronary heart disease in the non-diabetic population has been found to be amenable to correction (763, 764). The question of the long-term effects of lipid lowering agents in diabetes mellitus needs to be urgently addressed.

Retinopathy: I did not specifically attempt to corroborate previous suggestions that glycaemic control, blood pressure, and smoking were important determinants of retinopathy (7-9, 40, 584, 604, 605, 611), but did find that proliferative retinopathy was initially more common in long standing cases of IDDM if residual C-peptide secretion was absent. This difference was no longer apparent after one or two years of observation, so that even if one accepts that loss of endogenous insulin reserve leads to poorer glycaemic control and consequently more severe retinopathy, it would appear that the increasing duration of diabetes overwhelmed any such disadvantage, a point made on previous occasions (7-9, 40, 604, 605).

The independent association between retinopathy and various markers of nephropathy is well known (7, 584, 604, 608), and I was able to demonstrate proliferative retinopathy more frequently

in IDDM accompanied by nephropathy. Whether or not this reflects underlying disturbances of coagulation and/or enhanced vascular permeability commonon to both complications would require further studies, but I could not provide support for the suggestion (605, 617) that insulin antibodies were implicated in either.

The higher Epstein Fenz anxiety ratings amongst those with serious retinopathy might have been anticipated since both Bradley et al (523) and I found that fear of visual loss understandably generated great concern amongst patients with IDDM, and Wulsin et al (546) suggested that visual impairment and/or laser photocoagulation lead to considerable stress, although they pointed out the lack of research in this area. Meanwhile there is a good argument for further education designed to convey to patients the optimistic outlook for retinopathy whilst reinforcing those aspects of self-management that might minimise deterioration of the retinopathy.

Nephropathy: An association between early diabetic nephropathy and hypertension was observed in this thesis and appears virtually indisputable (8, 9, 584, 626, 628), although the 'chicken v egg' argument remains. I did not find glycaemic control in relation to residual C-peptide secretion had a major bearing on the presence or progression of renal function, but other reports have testified to a role for hyperglycaemia and glycosylation in albumin excretion and renal tissue damage, at least during the phase of incipient nephropathy (15, 357, 630, 640, 651).

I have previously discussed the effect of diabetic nephropathy on lipid metabolism in IDDM. Potentially detrimental

effects of smoking (8, 584, 605, 611) and insulin antibodies (584) on diabetic renal disease were not apparent from my cross-sectional or longitudinal observations. However I was able to show that autonomic dysfunction could modify both sodium and albumin excretion in IDDM. I was only able to speculate as to the mechanism behind such observations, but a more recent study from Lilja et al (765) supports the concept that autonomic neuropathy might modify the natural history of diabetic renal disease, and it may be more than coincidental that renal failure was the commonest reported cause of death in the study by Ewing et al (684) on the outcome in patients with autonomic neuropathy. Furthermore a close association between nephropathy and autonomic neuropathy has considerable implications for the management of systemic hypertension in patients with enhanced natriuresis and postural hypotension.

As with patients with large vessel disease, the lack of association between psychopathology and nephropathy may reflect a lack of awareness and concern about the implications of renal disease.

Neuropathy: I did not observe any significant alterations in symptoms or signs of peripheral or autonomic neuropathy following improvements in metabolic control, although poor glycaemic control has been linked with neuropathy in several other studies (37-40, 640, 651), but this may reflect failure to cross the glycaemic threshold suggested by Young et al (40) which would have ameliorated the situation.

The most important accompaniment of both symptoms and signs

of peripheral neuropathy was more frequent abnormal anxiety and depression ratings. This does not necessarily imply that the relationship was one-way, but it appears reasonable to suggest that the high level of concern regarding amputation (Chapter 3) may have had some bearing on the psychological response to neuropathy.

Impotence: I did not specifically examine the role of ageing, glycaemia, ethanol intake, blood pressure and neuropathy in the present study, as others have previously testified to the independent impact of these factors on diabetic impotence (714, 715), but I was able to demonstrate higher depression ratings in impotent men, supporting the findings of Cavan et al (547).

Hypoglycaemia: In keeping with reports from Dusseldorf, intensified conventional therapy aided by home blood gluose monitoring, was not accompanied by an excess of hypoglycaemia, although I did record that frequent hypoglycaemia was associated with a higher anxiety rating in the individual, as has been previously reported in the relatives of insulin dependent diabetics (544).

The work covered in this thesis covered several broad areas and understandably I have not reported every finding in detail.

I found that a programme of intensified diabetic management with regular access to the hospital could improve and maintain metabolic control, educational skills, and attitudes to diabetes, apparently without adverse effect other than a temporary increase in the number of contacts with health professionals. The

time course of the study was really too short to evaluate the impact of such a programme on the development and progression of complications, although this issue is to be addressed in the much larger DCCT study currently underway in the United States (766). It would appear from the current work that the DCCT and similar studies must address the effect of residual endogenous insulin secretion on metabolic control and also utilise different measures of glycaemic control to resolve fully the controversy regarding the role of glycaemia in the development of complications.

My studies on lipid metabolism show that 'metabolic control' in IDDM plays a relatively small part in determining levels of lipids and lipoproteins. Genetic and renal factors made a definite impact and hyperlipidaemia was shown to be a significant feature of IDDM. This work should provide the basis for further research designed in the first instance to demonstrate conclusively a build up of IDL in IDDM and to reveal the complete range of conformational abnormalities of lipoproteins, and the mechanism for dyslipoproteinaemia in early diabetic renal disease. Furthermore the evaluation of the relevance of fasting lipid estimations to diabetic vascular disease may be inappropriate since triglyceride-rich particles may be of vital importance, and they are obviously subject to modification by dietary intake.

The natural history of diabetic nephropathy and its relation to hypertension has still to be clarified, but the current work suggests that disturbed autonomic tone may be of some importance, and further studies of the effects of the autonomic nervous

system on renal haemodynamics and tubular function are undoubtedly required.

Finally, the impact of diabetic complications on the psyche has been underestimated. Those complications were loss of a faculty (vision, mobility, potency or consciousness) or of a job, which appear to lead to definite adverse changes in psychological status. Future programmes of diabetic care should recognise this and provide appropriate education and access to psychological counselling. Collaborative research in this area between diabetologists and psychologists would now appear to be a priority.

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CHAPTER 1 INTRODUCTION

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CHAPTER 2 DETERMINANTS OF METABOLIC CONTROL

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CHAPTER 3. EPIDEMIOLOGICAL AND PATHOPHYSIOLOGICAL ASPECTS OF VASCULAR AND NON-VASCULAR COMPLICATIONS

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APPENDIX I

TRIAL EVALUATION FORMS

Glucose Meter Trial - Entry Form

.....First Names.....Sex M ... F

No./Date of Birth.....

completion of form..... Case Number.....

trial entry..... Trial No.....Group A Glucose Mete B Urine Glucos

dress..... Telephone Number .....

..... Weight .....

..... Height .....

onset of Diabetes (years) ..... Duration on trial entry (years) ....

s Oral Hypoglycaemic Therapy YES/NO.....

---

rapy

ılin - length of treatment (years) .....

rent Insulin dose:-

	First	Second	
a.m.			Before 'tightening up'
p.m.			
p.m.			
a.m.			After 'tightening up'
p.m.			
p.m.			

l 'exchanges'

re:Breakfast a.m. Snack Lunch p.m. Snack Tea/evening meal Supper

....

r:Breakfast a.m. Snack Lunch p.m. Snack Tea/evening meal Supper

....

ıtient's Assessment of Own Control and Knowledge of Diabetes

Patient's Goals

Why do you think it is important to attend a diabetic clinic?

.....

Give me your own definition of diabetes

.....

Provided you feel well, how important do you believe it is to have as normal an average blood glucose level as possible?

Very/Quite/Not at all

a b c

Medication

Where is injection given? ARMS LEGS BUTTOCKS ABDOME

Do you rotate sites? .....

Any lumps or pitting at sites? .....

Who gives your injection? .....

Does anyone else in your family know how to give your injections? .....

Where do you keep your insulin? .....

What type of equipment do you use? Glass ..... How do you care for it? .....

.....

Disposable .....

Do you have any difficulty drawing up the correct amount of insulin or giving the injection? .....

Show me exactly how you draw up and give your injection.

Exercise : Type of activity

Morning: .....

Afternoon: .....

Evening: .....

What are your usual hours of sleep? .....

How does your schedule vary from day to day? .....

Name.

Diet History

Are you following a certain number of calories? .....

How many? .....

Have you had diet instruction in the past? .....

Do you eat three meals a day? .....

Do you eat between meals? .....

Who prepares your meals? .....

How often do you eat out? .....

Where do you eat out? .....

What times of day do you eat? .....

If included in your meal plan, is it practical to eat a morning, afternoon and evening snack? ..... If not, why not?

Why do you eat?

Good nutrition ..... Frustration .....

Hunger ..... Depression .....

To please others ..... Boredom .....

Social obligation .....

Do you eat : Milk ..... Fresh fruit ..... Vegetables .....

Eggs ..... Meat/Fish .....White/Wholemeal Bread.....

How well do you think your diabetes has been controlled during the past year? (circle

Excellent, good, fair, terrible

Urine testing

Do you check your urine for sugar? .....

What method do you use? Clinistix .....

Diastix .....

Clinitest .....

How often do you test? .....

Do you test before or after meals? .....

Do you empty your bladder first, void after 15 - 30 mins. later and test the second specimen? .....

Show me (or tell me) how you check your urine .....

Do you check for acetone or ketones? ..... When ? .....

.....

Show me (or tell me) how you check for this .....

Do you record your test results? .....

Most common result? 0, $\frac{1}{4}$, $\frac{1}{2}$, 1, 2?

Blood Sugar Regulation

(a) Low blood sugar (hypoglycaemia)

Name 5 symptoms of low blood sugar .....

Have you ever had symptoms of low blood sugar? .....

How often do you take hypos? (daily, weekly, monthly, less often) (Circle)

What time of day? Morning Afternoon Evening Night (Circle)

What symptoms did you have? .....

What action did you take? .....

Why do you think these reactions occurred? .....

Can you tell when you are going hypo in time to take action - always, usually, nev
(circle)

Do you always carry some form of sugar on you for emergencies? .....

What type? .....

Do you always have some form of diabetic identification with you? .....

What is glucagon? .....

b) High blood sugar (hyperglycaemia)

What is ketoacidosis? .....

Have you even been in ketoacidosis? .....

Name 5 symptoms of ketoacidosis? .....

Do you ever show ketones in your urine? .....

When was the last time they appeared in your urine? .....

What do you do if you become ill?.....

What symptoms of high blood sugar have you had? .....

Why do you think you had a ketoacidotic episode? .....

What action did you take? .....

Do you feel that you have accepted the fact that you have diabetes? .....

In what ways? .....

Do you feel depressed, hostile, fearful or angry about having diabetes?(circle)

Do you have any special concerns about diabetic complications?.....

.....

Have you had a significant loss, or change in your life or family life in the past one to two years?

Death ..... Move ..... Retirement .....

Divorce ..... Separation ..... Loss of Job .....

Change of job ..... Other .....

Had a serious illness or injury in past 1 - 2 years .....

Do you know anyone else who has diabetes?

How many days of work or school have you missed in the past year due to diabetes?

.....

Reasons .....

Have you been hospitalised for your diabetes? .....

When? .....

Circumstances? .....

Do you examine your feet each day? .....

How? .....

Why do you think foot care is important for diabetics? .....

ective Measurements -- before 'tightening up'

i) 24 hour urine glucose ..... m/mol 24h (date).....

Spot urine Albustix ..... mg/100 ml (date).....

24 hour urine albumin..... { mg/ (day).....mg/ 'night).... }

24 hour urine microalbuminurea (storage).... { TOTAL:...../24 hours }

Serum urea .....mMol/L Urine Creatinine mMol/24hr

Serum creatinine .....mMol/ Creatinine clear. .....mL/min.

Fasting serum chlorestero!.....

Fasting serum Triglyceride.....

C peptide levels postprandial (sent).....

Lipoproteins HDL ..... } mmol/L

APOB ..... mg/DL }

LDL ..... }

HDL2 ..... }

HDL3 ..... }

Home blood glucose profile (mMol/L)

	Breakfast			Lunch			Tea/Dinner			L
	0	1	2h	0	1	2h	0	1	2h	
Initial										
End of 'tightening up'										

- Hb A_1c - basal % (before 'tightening up')
- G.S.A. - basal % (before 'tightening up')

N.B. Aliquots of urine (2 x 5 ml) glucose meter trial box on 5 day ward, to be kep in deep freeze.

---

ocial Circumstances:-

ccupation ..... Social "Class" .....

arital state .....

hildren (ages) .....

ttitude to diabetes of partner .....

ttitude to diabetes of parents .....

moking: Cigarettes (number per day) .....
Pipe (ounces of tobacco per week) .....

lcohol: Type ..... Amount ..... (None 0, Mild 1, Moderate 2, Excessive 3)

rugs: .....

ast Medical History .....

ther relevant details .....

---

abetic Sister's Educational Assessment: (Excellent 1, Good 2, Fair 3, Poor 4, Terribl 5

	General	Insulin Injection/Dosage	Hypos	Use of Glucagon	Diet	Exercise	Illn
- up'							

-
up'

chniques:	Insulin Injection	Urine testing (diastix)	Blood glucose monitoring
'tightening up'			
'tightening up'			

Doctor's assessment of probable blood sugar control in past year

Excellent	Good	Fair	Poor	Terrible
1	2	3	4	5

linical State	Symptoms (0-none, 1-mild, 2-mod., 3-severe)	Physical Signs	*Bruit
		Peripheral Vascular	(R) (L)
ardiovascular		Femoral	
		Popliteal	
Cardiac	Angina	Post Tib.	
	Dyspnoea	Dors. Ped.	
Peripheral Vascular	Leg-skin ischaemic		
	Claudication	SBP/ DBP	ANS SCORE
	Hypotension	BP lying	.....
	Oedema	1. standing	.....
		2. handgrip	.....
		3. HR variation with deep breathing	.....
		4. HR standing	.....
ANS	Erectile impotence	5. HR valsalva	.....
		TOTAL	.....
spiratory	Cough	Chest:	
urological		Condition of Feet (R) (L)	
Peripheral Neuropathy	Paraesthesiae	R L 0 1 2 3 - -+ ++ +++	
Stroke		Ankle Jerks	
Other	Weakness	Vbrn.Sense	
		Fine Touch	
		Pin Prick	
isual	Refractive problems poor control?	Acuity (snellans) with glasses (R) (L)	
		Cataract (0 - 4)	
		Fundoscopy (0 - 4 each) Microaneurysms	
	Other	Haems	
		Exudates	
		New Vessels	
		Ret. proliferans	
		Opthalmological assessment (date)	
		Opthalmological treatment (date)	
		Pupillary Reaction:	

24 HOUR URINE COLLECTION

DAY TIME: From ..... Until ..... Volume ..... (-5ml)

NIGHT TIME: From .. .. Until ..... Volume ..... (-5ml)

TOTAL 24 HOUR VOLUME Volume ..... (-5ml)

5 ml ——> 24 hour urine glucose

2 x 5 ml ——> microalbuminuria

Residual volume ——> 24 hour creatinine clearance

CXR

ECG

			Meter	Lab.
enal	Polyuria Nocturia Dysuria Infections	Corellation Blood Sugar		
		Renal Threshold	Urine	Blood

ychology (separate profile sheet)

---

eck List

Trial Onset Date:

es patient understand the nature of the trial, and that there is an equal chance that ... will be allocated to glucose meter or control groups for one year? YES/NO

ce control has been improved as much as practicable, with short-term use of all means ilable, the patient is ready to be included in the trial.

eck Have you - Completed trial document?

- Completed Education/re-education?
- 24h urine Glucose - collected sample - deepfreeze on F1?
- HbA1c - sent sample to lab?
- Checked Baseline 10-point profile - and optimised treatment?
- Checked Blood glucose) technique?
- Checked Urine glucose)

ient's Consent

.....agree to take part in the Salford blood glucose monitor al, the nature of which has been explained to me by Dr .....

Signed .....

Witness .....

standing Problems

ONE YEAR GLUCOSE METER TRIAL FOLLOW-UP DOCUMENT

Surname ..... First Names ..... Sex M F

HPI No./date of Birth ..... Case Number .....

Date of Completion of Form ..... Trial Number ..... Group

Weight..... Kg.

Insulin dosage .....

Total contacts with hospital/clinic in 1 year:- .....

Total visits to hospital/clinic in 1 year:- .....

Total days of work in 1 year:- .....

Due to diabetes:- .....

Due to other causes:- .....

Hypo attacks:- monthly rate over last 3 months .....

FINGER PRICK PROFILES:-

Month	Own Results			Lab Results			Paired Analy	
	Mean BS/MUS	FBS/FUS	M Value	Mean BS	FBS	M Value	Number Suitable	Co at
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								

TWO YEAR GLUCOSE METER TRIAL FOLLOW-UP DOCUMENT

ırname ..... First Names ..... Sex M F

'I No./date of Birth ..... Case Number .....

ıte of Completion of Form ..... Trial Number ..... Group A(B(

Weight..... Kg.

sulin Dosage .....

)tal contacts with hospital/clinic in 1 year:- .....

)tal visits to hospital/clinic in 1 year:- .....

)tal days off work in 1 year:- .....

Due to diabetes:- .....

Due to other causes:- .....

/po attacks:- monthly rate over last 3 months .....

INGER PRICK PROFILES:-

onth	Own Results			Lab Results			Paired Analysis	
	Mean BS/MUS	FBS/FUS	M Value	Mean BS	FBS	M Value	Number Suitable	Correlation
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								

24h Urine Glucose .....

HbA1c ..... Glycosylated Albumen .....

Spot urine albustix ..... (mg/100ml)

24 hour urine proteinuria TOTAL ..... Correlation Blood Sugar .....Meter

CONC^{N} ....Lab.

24 hour urine microalbuminuria DAY .....

NIGHT .....

TOTAL .....

Serum Urea .....mmol/L Urine creatinine .....mmol/L

Serum creatinine .....mmol/L Urine creatinine ..... TOTAL (mmol/24 hr

Creatinine clearance .....mmol/min.

Fasting serum triglyceride .....

Fasting serum cholesterol .....

LDL .....

HDL .....

HDL_2 ..... mmol/L

HDL_3 .....

APOB ..... mg/DL.

CPeptide ..... pmmol/mL

:: total 'exchanges'

Breakfast	a.m. Snack	Lunch	p.m. Snack	Tea/Evening meal	Supper
.....	.....	.....	.....	.....	.....

ing: cigarettes per day ..... Stopped smoking (Yes/No) .....

pipe tobacco:ounces per week .....

hol: type ..... amount ..... (none 0, mild 1, moderate 2, excess. 3)

s: .....

ar Educational assessment by staff (Excellent 1, Good 2, Fair 3, Poor 4, Terrible 5)

General	Insulin Injection/Dosage	Hypos	Use of Glucagon	Diet	Exercise	Illness
....	....	....	....	....	....	....

Techniques:	Insulin Injection	Urine Testing (diastix)	or	Blood glucose monitoring
....	....	....		....

Doctor's assessment of probably blood sugar control in past year

Excellent 1	Good 2	Fair 3	Poor 4	Terrible 5

linical State	Symptoms (0 - none, 1 - mild, 2 - mod., 3 - severe	Physical Signs	*Bruit
		Peripheral Vascular	R L
		Femoral	
ovascular		Popliteal	
Cardiac	Angina	Post Tib.	
	Dyspnoea	Dors. Ped.	
pheral scular	Leg-skin ischaemic		
	Claudication	SBP/ DBP	ANS SCORE
	Hypotension	BP lying	.....
	Oedema	1.standing	.....
		2.handgrip	.....
		3.HR variation with deep brthing	.....
		4.HR standing	.....
ANS	Erectile Impotence	5.HR valsalva	.....
		TOTAL:	.....

atory	Cough	Chest

logical		Condition of Feet (R) (L)
ipheral copathy	Paraesthesiae	R L 0 1 2 3 - -+ ++ +++
oke er	Weakness	Ankle Jerks Vbrn. Sense Fine Touch Pin Prick

ual	Refractive problems poor control?	Acuity (snellans) R L with glasses Cataract (0 - 4) Fundoscopy (0 - 4 each)
	Other	Haems Exudates New Vessels
al	Polyuria	Ret. proliferans
	Polydypsia	Opthalmological Assessment (date)
	Nocturia	Opthalmological Treatment (date)
	Dysuria	Pupillary Reaction:
	Infections	

24 HOUR URINE COLLECTION:

DAY TIME: From ..... Until ..... Volume ..... (- 5 ml)

NIGHT TIME: From ..... Until ..... Volume ..... (- 5 ml)

TOTAL 24 HOUR VOLUME Volume .....(- 5 ml)

5 ml ⟶ 24 hour urine glucose

2 x 5 ml ⟶ microalbuminuria

Residual volume 24 hour creatinine clearance

CXR

ECG

METER GROUP - 1 YEAR QUESTIONNAIRE

) Do you feel that blood testing is more accurate than urine testing? YES / NO

) Do you feel that blood testing is more helpful than urine testing? YES / NO

) Do you wish to continue blood testing? YES / NO

If NO we will return you to urine testing ± filter papers.

If YES

) Would you be prepared to pay for the purchase of a meter if (a) sticks could be provided by the hospital

(b) sticks were not provided by the hospital

NOT

) Would you be prepared to enter the 2nd year of the study with a further equal chance of entering one of two groups:-

either using the meter (Group 1) or BM sticks alone (Group 2) in conjunction with filter papers to check which is most accurate for a 6 month peridd in each group.

/GCM

.8.84.

ZUNG

INSTRUCTIONS FOR QUESTIONS: BELOW IS A LIST OF THE WAYS YOU MIGHT HAVE FELT OR BEHAVED. PLEASE TELL ME HOW OFTEN YOU HAVE FELT THIS WAY DURING THE PAST WEEK.

	Rarely or none of the time (less than 1 day)	Some or a little of the time (1-2 days)	Occasionally or a moderate amount of time (3-4 days)	Most of the time (5-7 days)
I feel down-hearted and sad	0	1	2	3
Morning is when I feel the best	0	1	2	3
I have crying spells or feel like it	0	1	2	3
I have trouble getting to sleep at night	0	1	2	3
I feel that nobody cares	0	1	2	3
I eat as much as I used to	0	1	2	3
I still enjoy sex	0	1	2	3
I notice that I am losing weight	0	1	2	3
I have trouble with constipation	0	1	2	3
My heart beats faster than usual	0	1	2	3
I get tired for no reason	0	1	2	3
My mind is as clear as it used to be	0	1	2	3
I tend to wake up too early	0	1	2	3
I find it easy to do the things I used to	0	1	2	3
I am restless and can't keep still	0	1	2	3
I feel hopeful about the future	0	1	2	3
I am more irritable than usual	0	1	2	3
I find it easy to make decisions	0	1	2	3
I feel quite guilty	0	1	2	3
I feel that I am useful and needed	0	1	2	3
My life is pretty full	0	1	2	3
I feel that others would be better off if I were dead	0	1	2	3
I still enjoy the things I used to	0	1	2	3

Name..... Age ..... Sex ..... Date .....

M.H.L.C. (J.K. Rev.)

Below are a number of statements about health and illness. Each item is a statement with which you may agree or disagree. Underneath the statement is a scale which goes from 'Strongly Disagree' to 'Strongly Agree' Would you read the statement. Then decide what you feel about it. Decide whether you agree or disagree with it. Decide how strongly you feel about it one way or the other. Then put a circle round one of the alternatives underneath it.

Here is an example of a question and an answer:

"I feel healthier in the summer than I do in the winter."

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	(Slightly Agree:)	Moderately Agree:	Strongly Agree:

Please answer each statement carefully. But do not spend too much time on any one item. Try to answer each statement separately. When choosing your answer do not be influenced by your earlier choices. Answer in the way that explains how you feel about the statements.

Thank you

F/up. 1/2

1. If I get sick, it is my own behaviour which determines how soon I will get well again.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

2. No matter what I do, if I am going to get sick, I will get sick.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

3. Having regular contact with my doctor is the best way for me to avoid illness.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

4. Most things that affect my health happen to me by accident.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

5. Whenever I don't feel well, I should consult a medically trained professional.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

6. I am in control of my health.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

7. My family has a lot to do with my becoming sick or staying healthy.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

8. When I get sick I am to blame.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

9. Luck plays a big part in determining how soon I will recover from an illness.

Strongly Disagree	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

10. Health professionals control my health.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

1. My good health is largely a matter of good fortune.

trongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

2. The main thing which affects my health is what I myself do.

trongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

3. If I take care of myself, I can avoid illness.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

4. When I recover from an illness, it's usually because other people (for example, doctors, nurses, family, friends) have been taking good care of me.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

5. No matter what I do, I'm likely to get sick.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

6. If it's meant to be, I will stay healthy.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

7. If I take the right actions, I can stay healthy

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

8. Regarding my health, I can only do what my doctor tells me to do.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

9. Generally I don't bother about trying to protect my health.

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

20. I really try to avoid illness

Strongly Disagree:	Moderately Disagree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

21. I work at keeping healthy and fit.

...ngly	Moderately ...agree:	Slightly Disagree:	Slightly Agree:	Moderately Agree:	Strongly Agree:

(Form E-F 1 3 72)

ame .....

ge .....Sex ..... Date .....

nstructions: The following are some statements on feelings, aydreams, attitudes, and behaviour. Read each statement and ecide how often it applies to you;

ircle '1' if the statement never applies to you;
'5' if you experience it almost all of the time;
se '2', '3' and '4' for inbetween ratings.

Never = 1
Rarely = 2
Sometimes = 3
Fairly often = 4
Nearly always = 5

few itmes may be difficult to answer by checking frequencies. or these, you may indicate how true or false the item is for you by sing '1' for "Definitely False", '3' for "Questionable", '5' for Definitely True", and '2' and '4' for inbetween ratings.

e honest, but do not spend too much time over any one statement. s a rule, first impressions are as accurate as any. re there any questions?

1

Never = 1
Rarely = 2
Sometimes = 3
Fairly often = 4
Nearly always = 5.

.	I am an easy going person	1 2 3 4 5
.	I have sensations of burning, tingling, or crawling in certain parts of my body	1 2 3 4 5
.	I feel chilly at temperatures that are comfortable to others	1 2 3 4 5
.	My feelings are easily hurt	1 2 3 4 5
.	I am either too hot or too cold and cannot get comfortable at a constant temperature setting	1 2 3 4 5
.	I have trouble getting my breath for no special reason	1 2 3 4 5
.	My mouth feels dry	1 2 3 4 5
.	I have feelings of panic for no special reason	1 2 3 4 5
.	I have pounding headaches in which I can feel a definite beat	1 2 3 4 5
0.	I am a relaxed person	1 2 3 r 5
1.	I clench my teeth when anxious	1 2 3 4 5
2.	I am troubled by discomfort in the pit of my stomach	1 2 3 4 5
3.	I worry about little things	1 2 3 4 5
4.	I have a hard time swallowing	1 2 3 4 5
5.	I become upset when I have to wait	1 2 3 4 5
6.	My skin becomes painfully sensitive	1 2 3 4 5
7.	I notice my heart pounding	1 2 3 4 5
8.	I take things hard	1 2 3 4 5
9	I grind my teeth in my sleep	1 2 3 4 5
0.	I am bothered with blushing	1 2 3 4 5
1	I am troubled by tension interfering with my speech	1 2 3 4 5
2	My finger tips or other extremities become cold	1 2 3 4 5
3.	I become irritable about little things	1 2 3 4 5

24.	I have pressure headaches in which my head feels as if it were in a vice, or as if there were a tight band around it	1 2 3 4 5
25.	When embarrassed, I break out in a sweat which annoys me greatly	1 2 3 4 5
26.	I take things in my stride	1 2 3 4 5
27.	I have trouble with my hand shaking while I write	1 2 3 4 5
28.	I would rather win than lose in a game	1 2 3 4 5
29.	I am troubled with diarrhoea	1 2 3 4 5
30.	I have pains in the back of my neck	1 2 3 4 5
31.	I suddenly feel hot all over, without apparent cause	1 2 3 4 5
32.	I am troubled with backaches	1 2 3 4 5
33.	I am a nervous person	1 2 3 4 5
34.	In the absence of physical action my heart beats rapidly	1 2 3 4 5
35.	My hand shakes when I try to do something	1 2 3 4 5
36.	I have stomach trouble	1 2 3 4 5
37.	I go to sleep without thoughts bothering me	1 2 3 4 5
38.	My head feels tender to the point that it hurts when I comb my hair or put on a hat	1 2 3 4 5 1 2 3 4 5
39.	My sleep is fitful and disturbed	1 2 3 4 5
40.	The muscles of my neck ache as if they were tied in knots	1 2 3 4 5
41.	I feel that I am about to go to pieces	1 2 3 4 5
42.	I am easily frightened	1 2 3 4 5
43.	I have frightening dreams	1 2 3 4 5
44.	I have trouble with muscles twitching and jumping	1 2 3 4 5
45.	I am bothered by dizziness	1 2 3 4 5

Have you completed all items?

LEYTON OBSESSIONAL CARD INVENTORY – FEMALE VERSION
(different wording for the Male Version is given at the end of the Appendix)

'Check' indicates that this word should be written on the back of the card; the operator deals with these three cards according to the 'instructions for users'. (**) indicates that a mark is put on the back of the card to show that it goes through to the resistance and interference stages.

SYMPTOM QUESTIONS

Thoughts

1. Are you often inwardly compelled to do certain things even though your reason tells you it is not necessary? (Check)
2. Do unpleasant or frightening thoughts or words ever keep going over and over in your mind? (Check)
3. Do you ever have persistent imaginings that your children or husband might be having an accident or that something might have happened to them? (**)
4. Have you ever been troubled by certain thoughts or ideas of harming yourself or persons in your family – thoughts which come and go without any particular reason? (**)

Checking

5. Do you often have to check things several times?
6. Do you ever have to check gas or water taps or light switches after you have already turned them off? (**)
7. Do you ever have to go back and check doors, cupboards or windows to make sure that they are really shut? (**)

Dirt and contamination

8. Do you hate dirt and dirty things?
9. Do you ever feel that if something has been used, touched or knocked by someone else it is in some way spoiled for you? (**)
10. Do you dislike brushing against people or being touched in any way? (**)
11. Do you feel that even a slight contact with bodily secretions (such as sweat, saliva, urine, etc.) is unpleasant or dangerous, or liable to contaminate your clothes or belongings? (**)
12. Do you worry if you go through a day without having your bowels open?

Dangerous objects

13. Are you ever worried by the thoughts of pins, needles, or bits of hair that might have been left lying about? (**)
14. Do you worry about household things that might chip or splinter if they were to be knocked or broken? (**)
15. Does the sight of knives, hammers, hatchets, or other possibly dangerous things in your home ever upset you or make you feel nervous? (**)

Personal cleanliness and tidiness

16. Do you tend to worry a bit about personal cleanliness or tidiness?
17. Are you fussy about keeping your hands clean? (**)

*18. Do you ever wash and iron clothes when they are not obviously dirty in order to keep them extra clean and fresh? (**)
19. Do you take care that the clothes you are wearing are always clean and neat, whatever you are doing? (**)
20. Do you like to put your personal belongings in set places or patterns? (**)
21. Do you take great care in hanging and folding your clothes at night? (**)

Household cleanliness and tidiness
*22. Are you very strict about keeping the house always very clean and tidy? (**)
23. Do you dislike having a room untidy or not quite clean for even a short time? (**)
24. Do you sometimes get angry that children spoil your nice clean and tidy rooms?
25. Do you like furniture or ornaments to be in exactly the same place always? (**)
26. Do your easy chairs have cushions which you like to keep exactly in position?
27. If you notice any bits or specks on the floor or furniture do you have to remove them at once before you are due to clean round? (**)
28. Do you ever clean or dust the rooms that haven't had time to get dirty, just to make sure that they are really clean? (**)
29. Do you ever have to dust, sweep, or wash things over again several times just to make sure they are really clean? (**)

Order and routine
30. Do you have to keep to strict timetables or routines for doing ordinary things? (**)
31. Do you have to keep a certain order for undressing and dressing, or washing and bathing? (**)
*32. Do you get a bit upset if you cannot do your housework at set times or in a certain order? (**)

Repetition
33. Do you ever have to do things over again a certain number of times before they seem quite right? (**)
34. Do you ever have to count things several times or go through numbers in your mind? (**)
*35. Do you ever get behind with the housework because you have to do something over again several times? (**)

Over-conscientiousness and lack of satisfaction
36. Are you a person who often has a guilty conscience over quite ordinary things?
37. Are you the sort of person who has to pay a great deal of attention to details? (**)
38. Are you ever over-conscientious or very strict with yourself?
39. Do you ever waste time by doing a thing more thoroughly than is really necessary just to see it is really finished? (**)
40. Even when you have done something carefully, do you often feel that it is somehow not quite right or complete? (**)
41. Do you feel unsettled or guilty if you haven't been able to do something exactly as you would like? (**)
42. Do you always fail to explain things properly, in spite of having planned beforehand exactly what to say?

Indecision
43. Do you have difficulty in making up your mind? (**)
44. Do you have to turn things over and over in your mind for a long time before being able to decide about what to do? (**)
45. Do you ask yourself questions or have doubts about a lot of things you do? (**)
46. Are there any particular things that you try to keep away from or that you avoid doing, because you know that you would be upset by them? (**) (Check)

TRAIT QUESTIONS
Hoarding
47. Do you find it difficult to throw things away? (**)
48. Do you keep rather a lot of empty boxes, paper bags, old newspapers, or empty tins in case they come in useful one day? (**)
*49. Does your stock of soap, detergents, or cleaning materials ever get large because you find yourself buying more than you actually use?

Cleanliness
50. Do you regard cleanliness as a virtue in itself?

Meanness
51. Do you get more pleasure from saving money than from spending it?
52. Are you more careful with money than most people you know?
53. Do you keep regular accounts of the money you spend every day?

Irritable and morose
54. Do you usually look on the gloomy side of things?
55. Do people often get on your nerves and make you feel irritable?
56. When you feel critical of someone, do you usually say what you are thinking?

57. Do you get angry or irritated if people don't do things carefully or correctly?

Rigidity

58. Do you try to avoid changes in your house or work or in the way you do things?
59. Do you try to avoid changing your mind once you have made a decision about something?
60. Are you a person who likes to stick to principles and decisions whatever the opposition or difficulties?
61. Do you pride yourself on thinking things over very carefully before making decisions?

Health

62. Do you think that regular daily bowel movements are important for your health?
63. Do you often get scared that you might be developing some sort of serious illness or cancer?

Regularity

64. Are you very systematic and methodical in your daily life?
65. Do you like to get things done exactly right, down to the smallest detail?
66. Do you think it is important to follow rules and regulations exactly?
*67. Do you like to have set times or orders for doing your household jobs?

Punctuality

68. Are you ever late because you just can't seem to get through everything in time? (**)
69. If you have to catch a train or keep an important appointment, do you have to plan out how to do it beforehand in great detail? (**)

CHANGES IN WORDING FOR MALE VERSION

18. Becomes: Do you ever ask to have clothes washed or cleaned that are not obviously dirty in order to keep them extra clean and fresh? (**)
22. Becomes: Are you strict about the house always being kept very clean and tidy?
28. Becomes: Do you often do any dusting or cleaning at home without being asked to do so? (**)
29. Becomes: Do you ever have to clean or wash things over again several times just to make sure they are really clean? (**)
32. } Substitute 'work' for 'housework'.
35. }
49. Omit
67. Becomes: Do you like to have set times or orders for doing your work?

QUESTIONS OMITTED

The following questions were in the first version used, but were omitted after approximately 100 subjects had been seen. Both high and low scorers answered 'yes' to these questions to the same extent. (The numbers are those in the original version.)

3. Do you ever get tunes, numbers, or words running through your mind that you can't get rid of for a while?
9. If you have to add up columns of figures or sums of money, do you have to do it more than twice before you can accept it as correct? (**)
22. Do you fail to keep your own things neat and tidy, even though you try?
27. Do you have a room in which children are not allowed alone for fear of disturbing or dirtying things?
35. Do you make lists of things you have to do?
41. Do you ever have to stop a moment to work things out in your mind before being able to go on and do something else? (Check)
53. Is there anything that you avoid doing because you know that even if you try you won't feel satisfied that you've done it properly? (**)
55. Do you accumulate a lot of old things just in case they might come in useful one day? (**)
57. When you go shopping do you tend to buy more of a thing than you actually need? (Check)
58. Do you ever find yourself buying more tinned or packaged goods than you really need?
60. Are you a very tidy person?
66. Do you get fed up with people who are always bright and cheerful?
67. Do you think that in general it is foolish to be optimistic?
81. Do you do things or keep appointments exactly on time?
83. Do you ever get to stations or appointments too early and have to wait rather than risk being late? (**)

RECORD

of

The Mill Hill Vocabulary Scale, Form I Senior

(1977 Revision)

and the

Standard Progressive Matrices Sets A, B, C, D & E

Name ..... *Date* .....

Age ..... *Birth Day* ..... *School or Occupation* .....

Synonyms .... *Time* .....

Definitions .... *Time* .....

.....

P.M. Score .... *Time* .....

.....

Other Tests

....

....

....

....

Notes

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STANDARD PROGRESSIVE MATRICES

It begun_____ Test ended_____

A			B			C			D			E		
1			1			1			1			1		
2			2			2			2			2		
3			3			3			3			3		
4			4			4			4			4		
5			5			5			5			5		
6			6			6			6			6		
7			7			7			7			7		
8			8			8			8			8		
9			9			9			9			9		
10			10			10			10			10		
11			11			11			11			11		
12			12			12			12			12		

Time	Total	Grade

Notes

Tested by_____

G.P. 77 120,000

SET B

In each group of six words below underline the word which means the same as the word in heavy type above the group, as it has been done in the first example:

Begun .....

1 **MALARIA**
basement fever
theatre fruit
ocean tune

2 **FASCINATED**
ill-treated modelled
poisoned charmed
frightened copied

3 **LIBERTY**
freedom worry
rich serviette
forest cheerful

4 **ANONYMOUS**
applicable magnificent
nameless fictitious
insulting untrue

5 **STUBBORN**
steady obstinate
hopeful hollow
orderly slack

6 **PROSPER**
imagine propose
trespass beseech
punish succeed

7 **PRECISE**
natural stupid
faulty grand
exact small

8 **RESEMBLANCE**
likeness fondness
assemble repose
attendance memory

9 **SCHOONER**
building man
scholar singer
plant ship

10 **ELEVATE**
revolve move
raise work
waver disperse

11 **COURTEOUS**
dreadful proud
polite short
curtsey truthful

12 **RUSE**
limb paste
colour burn
trick rude

13 **LAVISH**
unaccountable selfish
romantic extravagant
lawful praise

14 **IMMERSE**
frequent hug
dip reverse
rise show

15 **CONCILIATE**
congregate pacify
reverse radiate
compress strengthen

16 **ENVISAGE**
enfeeble activate
surround estrange
contemplate regress

17 **AMULET**
charm jacket
flirtation crest
cameo savoury

18 **GARRULOUS**
talkative daring
massive ugly
ridiculous fast

19 **LIBERTINE**
missionary rescuer
farrago canard
regicide profligate

20 **BOMBASTIC**
democratic pompous
bickering cautious
destructive anxious

21 **LEVITY**
parsimony velleity
salutary frivolity
alacrity tariff

22 **WHIM**
complain noise
fancy tonic
wind rush

23 **RECUMBENT**
fugitive cumbersome
unwieldy repelling
penitent reclining

24 **QUERULOUS**
astringent fearful
petulant curious
inquiring spurious

25 **TEMERITY**
impermanence rashness
nervousness stability
punctuality submissiveness

26 **FECUND**
esculent optative
profound prolific
sublime salic

27 **ABNEGATE**
contradict decry
renounce execute
belie assemble

28 **TRADUCE**
challenge attenuate
suspend establish
misrepresent conclude

29 **VAGARY**
vagabond caprice
obscurity vulgarity
evasion fallacy

30 **SPECIOUS**
fallacious coeval
palatial typical
nutritious flexible

31 **SEDULOUS**
rebellious dilatory
complaisant diligent
seductive credulous

32 **NUGATORY**
inimitable adamant
sublime contrary
numismatic trifling

33 **ADUMBRATE**
foreshadow protect
detect eradicate
elaborate approach

34 **MINATORY**
implacable diminutive
belittling quiescent
depository threatening

Ended .....

SET A

Write down in a few words the meaning of each of the following words as it has been done for the first word. Begun .....

1. Brag ..... Boast
2. Rage .....
3. Squabble .....
4. Connect .....
5. Provide .....
6. Mingle .....
7. Stance .....
8. Verify .....
9. Formidable .....
10. Thrive .....
11. Shrivel .....
12. Docile .....
13. Surmount .....
14. Sultry .....
15. Criterion .....
16. Latent .....
17. Dwindle .....
18. Construe .....
19. Efface .....
20. Trumpery .....
21. Virile .....
22. Perpetrate .....
23. Glower .....
24. Sensual .....
25. Obdurate .....
26. Palliate .....
27. Adulate .....
28. Felicitous .....
29. Ambit .....
30. Recondite .....
31. Cachinnation .....
32. Exiguous .....
33. Putative .....
34. Manumit .....

Ended .....

APPENDIX II

2. SYNOPSIS OF STATISTICAL TERMINOLOGY AND METHODS

PARAMETRIC STATISTICS- Tests using parametric statistics presume that observations made in individuals are independent (i.e. selection of any one case from the population for inclusion in the sample should not bias the chances of other cases for inclusion, and must be drawn from normally distributed populations). Populations should have the same variance, and variables should have been measured in an interval scale so that the means of the populations are linear combinations (i.e. the effects are additive).

NON-PARAMETRIC STATISTICS - Tests using non-parametric statistics do not specify conditions about the parameters of the population from which the sample was drawn. Although it is assumed that the variables under study are independent and demonstrate continuity, these criteria are less important that for parametric testing. Non-parametric statistics are relevant for analysis using small sample sizes, observations from several different populations, and data which is simply ranked (i.e. nil/background/proliferative retinopathy), or classificatory.

THE KOLMOGOROV-SMIRNOV ONE-SAMPLE TEST

This is a test of goodness of fit of data. It measures the degree of agreement between the distribution of a set of sample values (observed scores) and normal distribution for that variable. The test involves specifying the cumulative frequency distribution which would occur under the theoretical distribution and comparing it with the observed cumulative frequency

distribution. The point at which the theoretical and observed distributions show greatest divergence is determined. Reference to the sampling distribution determines whether the divergence is likely on the basis of chance. On the basis of this test, data is classified as normally distributed or otherwise and consequently parametric or non-parametric statistics are employed.

NON-PARAMETRIC TESTS

1. THE McNEMAR TEST - This test is designed to compare the significance of changes between 2 groups over a period of time. Subjects effectively serve as their own controls and 'nominal measurements' are used to assess the 'before to after change'.

2. WILCOXON 'MATCHED PAIRS' SIGNED RANKS TEST - The test utilizes information about the relative magnitude and direction of the differences within pairs, and gives more weight to a pair which shows a large difference between the 2 conditions than to a pair which shows a small difference. This test was used when measurements were in an ordinal scale both within and between pairs, and analysed repeated measurements over periods of time. Both the McNemar and the Wilcoxon Signed Ranks Test are applicable to studies involving 2 related groups. The following 3 tests are suited for use in a study design involving 2 independent groups.

3. FISHER EXACT PROBABILITY TEST - The test allows analysis of either nominal or ordinal discrete data when the two independent samples are small in size. It is used when the scores from two

independent random samples all fall into one or the other of two mutually exclusive classes (i.e. scored as one of two possible scores). Scores are represented as 'frequencies' in a 2 x 2 contingency table. This test was employed to examine prevalences of complications in 2 independent samples (e.g. retinopathy in diabetics with or without proteinuria).

4. THE X^2 (CHI-SQUARED) TEST FOR TWO INDEPENDENT SAMPLES.

The test determines the significance of differences in frequencies between two groups, where the measurement involved may be as weak as nominal scaling. The hypothesis under test is that two groups differ with respect to some categorical characteristics and therefore with respect to the relative frequency with which group members fall in several categories. The test can be extended to measure the prevalence in more that two groups if corrected by Yates' continuity test (as in assessment of the observed prevalence of the Apolipoprotein E phenotypes in comparison to that expected according to Hardy-Weinberg equilibrium). The chi-squared test can best be used in such situations if fewer than 20% of the cells have an expected frequency of less than 5 and if no cell has an expected frequency of less than one, otherwise adjacent categories must be combined to increase the expected frequencies. For example, in the analysis of 81 healthy and 81 insulin-dependent diabetic men, the Chi-squared test was employed to assess any difference in the prevalence of hyperlipidaemia between the 2 groups.

5. THE MANN-WHITNEY U TEST - This tests for the equality of means or variables between 2 independent groups, and is a

sensitive useful alternative to 't testing' for parametric data when data is likely to be 'distribution free', or when the actual measurement was weaker than the interval scaling. It was used for all but very small sample sizes, and is more resistant to distortion by 'rogue' values than the t test, and therefore more useful when dealing with clinical data.

6. THE KRUSKAL-WALLIS 1-WAY ANALYSIS OF VARIANCE - This was used when comparing more than 2 groups of data with continuous variables and ordinal measurement of these variables. It assesses whether 3 or more groups where sample values differ are genuinely different population differences or whether they represent merely chance variations such as are to be expected among several random samples from the same population.

7. SPEARMAN RANK CORRELATION COEFFICIENT - The correlation coefficient gives a measure of the degree of association between variables where both are measured on an ordinal scale. Values are replaced by rankings and the test is more robust than the Pearson correlation coefficient against non-normalised data distribution (V.I.) The statistic attained 'rho' is represented as r_s.

8. KENDAL RANK CORRELATION COEFFICIENT - This statistic is designated tau (r), and measures correlation with the same sort of data for which r_s is used if ordinal measurement of both X and Y variables has been achieved. r can be generalised to a partial correlation coefficient unlike r_s, when there is a possibility that the correlation is due to the association between each of the two variables and a third variable.

PARAMETRIC STATISTICS

1. PAIRED AND UNPAIRED STUDENT'S 't' TEST

These tests compare the mean values between 2 populations and compare the difference in amount of scatter if data is normally distributed in both populations. Unpaired t testing is used more often in reponse to intervention with for example education and home blood glucose monitoring. Therefore it would be appropriate to utilise paired testing to compare the outcome of the initial intensive management during the run-in period, whilst unpaired t testing would be more appropriate in assessing difference between blood and urine testing in the two groups.

2. PEARSON'S CORRELATION COEFFICIENT

If data is categorical the Pearson's product movement correlation coefficient can be employed where the significance pertaining to this would be the P value of the corresponding t test. Whilst the measurement is therefore less reliable, it can still be quoted as an index of non-independence of sex and height. The Pearson correlation coefficient for continuous data requires parametric measurements in at least an equal interval scale. In small samples the Spearman's test would be more appropriate.

STEPWISE MULTIPLE REGRESSION (MULTIVARIATE) ANALYSIS - In this procedure a variable is expressed as a weighted sum of 'predictor' variables, to assess independent associations between variables. The stepwise procedure starts by taking the predictor variable which correlates best with the test variable, and then adding others successively, until addition of further variables

does not improve the prediction of the test variable. If the predictor variables are themselves correlated, the method automatically chooses the correct weights, so that the contribution of each predictor to the test variable is found. If a particular variable 'wants' to come into the equation in preference to another, then the former must be more closely related to the test variable, even after correction for the latter.