# ABSTRACT SERVICE

**Umesh Dashora and Hemraj B. Chandalia**

## ETIOLOGY

### Residue 57 of HLA-DQ B-chain as a risk determining factor of IDDM in Finland.

*Helena Raijonen, Jorma Llonen, Mikael Knip, Hans K Akerblom, Oulu and Helsinki, Finland.*

It has been proposed that negatively charged aspartic acid at position 57 of HLA-DO B-chain determines the resistance of developing IDDM while the genetic susceptibility correlates with a neutral amino acid residue (Ala, Ser, Val). The disease rate is very low in Oriental populations having a high frequency of Asp57.

This arises a question whether the high incidence rate of IDDM in Finland could be explained by the distribution of this disease marker. In the present study the PCR products of 66 diabetic patients and 109 control subjects were analyzed with six sequence specific oligonucleotide probes. Only 11% of diabetic phenotypes were typed as Asp57 which suggests that ASp57 negativity is a definite risk marker for developing IDDM also in Finnish patients. However, the susceptibility conferred by non-Asp haplotypes is not equally strong: Dow8 is the most dominative one as a risk marker (DQw8 > DQw2 >DQw5). Correspondingly, the frequency of DQw6 was more strikingly decreased among IDDM patients than that of DQw7 and DQw9. In the control subjects the frequency of Asp57 positive phenotypes was 78% which is higher than in several Caucasian populations with lower IDDM figures. To conclude, the disease risk is not defined only by Asp57 and it cannot explain differences in disease rates of various Caucasian populations.

| | DM without PC (n = 423) | FCPD (n = 75) |
|---|---|---|
| Father | 61 (14.4%) | 2 (2.7%) |
| Mother | 16 (3.8%) | 1 (1.3%) |
| Both Parents | 2 (0.5%) | 0 (0.0%) |
| Brother | 19 (4.5%) | 4 (5.3%) |
| Sister | 2 (0.5%) | 1 (1.3%) |
| Others | 33 (7.8%) | 3 (4.0%) |
| unknown | 86 (20.3%) | 28 (37.3%) |
| More than one diabetic in a family | 37 (8.7%) | 0 (0.0%) |
| Negative | 204 (48.2%) | 36 (48.0%) |

### FCPD-Environmental or genetic?

*H. Mahtab, N.G. Banik, Abul Ahsan, Faruque Pathan and A. K. Azad Khan*

*Bangladesh Institute of Research & Rehabiliation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM), Ibrahim Memorial Diabetes Centre, Dhaka.*

In a prospective study of 498 young diabetics (< 30 years) 75 were found to have pancreatic calcification and they were labelled as fibrocalculous pancreatic diabetes (FCPD). The family history of diabetes was analysed in all of them. The results are shown in the table.

The family history data strongly suggest that genetic factors are less important in FCPD than in the general run of diabetics. This may mean that one or more environmental factors are of importance in the development of FCPD.

### Factors Contributing to the Development of IGT or DM in Offspring of Both Parents Diabetic.

*A.K Azad Khan, Ataharul Islam, & H. Mahtab*

*Bangladesh Institute of Research & Rehabilitation in Diabetes, Endocrine & Metabolic Disorders (BIRDEM), Ibrahim Memorial Diabetes Centre, Dhaka.*

The offspring of both parents diabetic are a special group of subjects with high genetic succeptibility to DM. Hence they offer special opportunity for studying factors contributing to the development of DM. We studied 559 such connubial offspring by subjecting them to standard OGTT.

They were categorised as normal, IGT or DM according to standard WHO criteria. We considered several characteristics such as sex, age, body wt. and education of the offspring, and body wt., age at detection of DM and treatment-group of parents to identify the factors contributing to development of DM in the connubial offspring.

Out of 559 connubial offspring 28 had IGT and 89 had DM. Linear logistic regression was the statistical technique used to measure the influence of the different factors in the development of DM and IGT.

It was observed that the variables exerting significant effect on IGT and DM were age of connubial offspring (P= 0.0041) and age at detection of mother's DM (P= 0.0013). The results also were in favour of IGT being an intermediate stage between normal and DM.

### HLA-DQA1*1 Gene Contributes to Resistance and HLA-DQA1*3 Gene Confers. Susceptibility to Insulin Dependent Diabetes Mellitus in Japanese Subjects.

*K Yamagata, T. Hanatusa, H. Nakajima, N. Kono, and S. Tarui, Osaka, Japan.*

Several genetic backgrounds contribute to the pathogenesis of IDDM, and human leukocyte antigen (HLA) gene is an important candidate. To Clucidate the role of HLA genes in Japanese IDDM, DQB1, DQA1 and TNF-β genes were investigated.

DNA of twenty-two Japanese IDDM patients and thirty-two control subjects were amplified by polymerase chain reaction. Amplified DNA was subjected to allele specific oligonucleotide dot blot analysis, restriction fragment length polymorphism analysis and DNA sequencing.

First, 50% IDDM patients were homozygous foraspartic acid, implying that aspartic acid at position 57 of HLA-DQB chain could not protect sufficiently against IDDM in Japanese. In contrast, DQwl.2 had protective effect against the disease. Second, all investigated IDDM patients had DQA1*3 allele and 77% patients were homozygous for DQA1*3 allele. DOA1*3 sequences of IDDM patients were

identical to the normal one. The frequency of this allele was significantly increased (p=0.000) in IDDM.

Particularly, DOA1*3 was found unexpectedly on both alleles even in two patients who have neither HLA-DR4 nor DR9. Third, DQA1*1 allele was significantly decreased (p=0.001) in IDDM. Fourth, polymorphism of TNF gene to Ncol digestion had no correlation with Japanese IDDM in contrast to caucasian IDDM. These results strongly suggest that HLA-DQA1 gene contributes to susceptibility and resistance to Japanese IDDM.

## PATHOPHYSIOLOGY

### The role of calcium on the effects of amylin in incubated skeletal muscle.

*Brendan Leighton, Clive Da Cosia and Elizabeth Foot. Oxford, England.*

4Amylin is secreted from the pancreatic β-cells. Amylin has about 50% sequence homology with the 37 amino acid neuropeptide CGRP. Amylin is a potent inhibitor of basal and insulin mediated glycogen synthesis in isolated incubated rat soleus muscle. CGRP at low levels (1-10 nM), inhibits glycogen synthesis but does not increase the content of cyclic AMP in muscle. Therefore, we investigated the role of calcium in amylin effects in skeletal muscle. Rat soleus muscle was incubated in the presence of amylin (10 nM) and various calcium concentrations (0.31, 1.2, 18, 500 and 1000 µM made with calcium/EGTA buffers). Amylin did not inhibit insulin-stimulated glycogen synthesis when the concentration of calcium was at 1.2 or 0.31 µM. The effect of the calcium ionophore A 23187 (10 µM), which increases the rate of entry of calcium ions into cells, on insulin-mediated glucose metabolism was measured in isolated incubated soleus muscle preparations. A 23187, like amylin, inhibited both basal and insulin stimulated glycogen synthesis. It has yet to be determined if calcium ions are directly involved in the mechanism of action of amylin in muscle.

### Diabetes Mellitus in young is not related to undernutrition in rural Indian populations.

*P.V Rao and M.M.S. Ahuja,*
*All India Institute of Medical Sciences, New Delhi.*

Among those screened for diabetes mellitus (DM) at five rural centers during 1989 in India, there were 5342 persons (male 2553 and female 2789) between 15 and 34 years of age. All subjects, with two-hour capillary whole blood glucose exceeding 139 mg/d1 after 75gm oral glucose, were retested for both fasting and two- hour blood glucose and diagnosed as per WHO criteria.

Prevalence rate for newly diagnosed DM was 0.19% (0.27% male, 0.11 % female), for previously known DM was 0.06%, and for impaired glucose tolerance it was 0.04% in this population below 35 years of age. Undernutrition defined as body mass index (BMI) ($Wt/Ht^2$) below 19 was noted in 1515 male and 1558 female subjects. Out of them, 3 male and 1 female diabetics were newly diagnosed as against 4 male and 2 females among those with BMI ≥ 19. Mean BMI was not significantly different between normal and newly diagnosed DM in either sex (normal vs. DM = male, 18. 6 ± 2.7 vs. 19.7 ± 3.5; female, 18.9 ± 2.7 vs. 19.9 ± 2.8). In this large rural population study, undernutrition could not be related as a possible risk factor for developing DM in young.

### Prolonged Incubation of Skeletal Muscle in Vitro Enhances Insulin-Stimulated, But Not Hypoxia - Stimulated, Glucose Transport.

*E.A. Gulve*, G.D. Cartee*, K.J. Rodnick, and J.O. Holloszy**
*St. Louis, MO.*

We previously found that prolonged incubation of muscle in vitro in Krebs-Henseleit buffer containing 8 mM glucose leads to large increases in glucose transport activity, as assessed with 3-0methylglucose (3MG). Incubation of rat epitrochlearis muscles for 9h led to 3-to 6-fold increases in both basal glucose transport and in transport measured in the presence of submaximal insulin (0.2 nM). Glucose transport in skeletal muscle can be activated by two separate pathways; one is activated by insulin, the other by hypoxia and contractile activity. In the current study we examined the effect of prolonged incubation on the maximal capacities of these two pathways. Incubation of muscles for 9h led to a two-fold greater increase in maximally insulin- stimulated transport. In contrast, the response to a maximal hypoxic stimulus was not altered by prolonged incubation. The increases in basal and insulin-stimulated transport were completely suppressed by cytochalasin B, indicating that they are mediated by glucose transporters. Muscle GLUT-4 content was not altered by prolonged incubation. The effects of maximal insulin and hypoxic stimuli were additive after short term incubations, as shown previously. In contrast, maximal effects of these two stimuli were no longer additive after 9h incubation. In summary, the increase in 3MG transport with prolonged incubation are specific for basal and insulin stimulated pathways and are not mediated by changes in muscle GLUT-4 content.

### Obesity in Diabetes Requires Sufficient Insulin Secretory Capacity.

*Jann Arends and Berend Willms, Bad Lauterberg, Germany.*

To investigate a possible relationship between B-cell secretory capacity and body weight, we analyzed data of 108 diabetic subjects after distribution into 3 subgroups: A = 33 patients with IDDM (age 38± 13 years); B = 31 patients with basal c-peptide (CP) < 0.33 nM and no clear diagnosis of IDDM or NIDDM (53± 17 years); C = 44 patients with NIDDM and basal CP ≥ 0.33 nM (58± 12 years). Mean age in A was lower than in B or C (P<0.01). HbA1 was similar in A =11.3, B = 11.3 and C = 11.7 %. Functional B- cell reserve was reduced in A and B, since insulin therapy was necessary in A = 100, B = 97 Versus C = 60 % of patients. Broca index and basal CP in C were higher than in A or B (p<0.01 ), but within C there was no correlation between CP and Broca index. Reduced β-cell reserve (group A + B) coincided with normal body weight (Broca index in A = 0.96, B = 0.97 versus C = 1.20) and obesity was rare in A and B as compared to group C (Broca > 1 .20 in A = 0, B = 3, C = 64% of patients). 45% of patients in B had experienced a large loss of weight in the preceding years, possibly in connection with decreasing B-cell function, others in B had never been obese. The body weight of most patients with basal CP ≥ 0.33 nM was above normal (95% of patients).

Conclusion: There seems to be a lower limit of residual B-cell secretory capacity that is necessary to allow for obesity in diabetic patients.

## Acute Hyperinsulinism Has No Effect On Fibrinolysis In Lean And Obese Subjects.

*B. Lormeau, X. Debussche, S. Gross, H. Puy, S. Fendri, J. Delobel., J. Ouichaud,*
*Amiens, France.*

Decreased fibrinolytic activity has been reported in chronic hyperinsulinaemic obese subjects but the effect of acute hyperinsulinism is not known. A three 2-hr steps hyperinsulinaemic euglycaemic clamp was performed in the morning (insulinaemia: 88 ± 19, 210 ± 40, and 1132 ± 100 mU/L) in 7 obese women (3 of whom diabetic with elevated basal C-peptide) and 6 lean controls (3F, 3M). The following parameters were determined at the end of each 2-hr step (TO,T2,T4 and T6) and 24 hrs later (T24): euglobin clot lysis time (ECLT: Von Kaula), tissue plasminogen activator antigen (tPA Ag: ELISA Imulyse tPA*), PAI activity (spectrolyse PL*). In all subjects, the normal diurnal variations were observed. In obese subjects, fibrinolytic activity was uniformly inhibited, with highly significant elevation of PAI throughout the clamp. ECLT, tPA Ag, and PAI in obese (vs controls) were respectively: at TO: 388 ± 55 min (vs 160 ± 20 min). 7.8 ± 1.4 (vs 5.0 ± 0.8 ng/ml), and 25.5 ± 6.4 (vs 4.8 ±0.9 U/ml; p <0.001 ); at T6: 370 ± 53 (vs 140 ± 20 min), 7,8 ± 1.7 (vs 3.7 ± 0.2 ng/ml), and 14.9 ± 5.3 (vs 1.4 ± 0.5 U/ml). At T24, values were not different from TO.

In conclusion: 1) before clamp, in chronic hyperinsulinaemic state fibrinolytic activity is decreased, because of an increase in PAI; 2) acute hyperinsulinism does not affect the diurnal variations of fibrinolytic activity in control and obese subjects.

## MRDM-Hospital incidence & hormonal adaptation as observed in Orissa.

*K.C. Samal, S. Das & B.B. Tripathy*
*S.C.B. Medical College, India.*

Among 8520 patients observed during 1980-89 at our diabetes clinic, 790 (9.2 %) had onset of diabetes by the age of 30 years, which includes 93(1.02%) patients with onset by 15 yrs. of age. MRDM accounted for 651 (82.4%) of the former and 36 (38.7%) of the latter. Protein deficient diabetes mellitus (PDDM) constituted 58.2% of the young onset (by 30 yrs) and 26.8% of the childhood onset diabetics while fibrocalculus pancreatic diabetes (FCPD) occured in 24.2% and 11.8% respectively. Serum insulin (IRI), hGH, LH, FSH, prolactin, $T_3$, and $T_4$ were estimated in 19 cases with MRDM. 10-PDDM & 9-FCPD) FBG as well as 2 hrs PGBG were very high in both groups of MRDM. IRI, particularly in response to oral glucose, was significantly lower (13.12 & 17.1 uu/ml) than normals (58.2uu/ml). Mean basal hGH was high ( >6ng/ml) compared to healthy controls and IDDM (3.1 ng/ml). There was paradoxical rise in hGH level following oral glucose, more so in PDDM (>8ng/ml). Levels of other hypophyseal hormones were within normal limits except prolactin which was high. $T_3$ and $T_4$ were lower than normal. Thus in both types of MRDM, PDDM in particular, the hormonal pattern was akin to that of non-diabetics with PEM. This provides further evidence in support of the possible role of malnutrition in the pathogenesis and clinical expression of MRDM.

## Are Epinephrine and Norepinephrine Ketogenic or Antiketogenic in Man?

*AJ Krentz, M MC Kinley, PJ Boyle, and DS Schade*
*Albuquerque, NM.*

The ketogenic role of epinephrine in normal man is controversial. We compared the ketogenic effects of epinephrine (E) and norepinephrine (NE) in healthy volunteers. Physiological protocol: Eight subjects each received 60 min infusions of E ( 10 ng.kg$^{-1}$ min$^{-1}$ ), NE (32.5 ng.kg$^{-1}$.min$^{-1}$), and fatty acid control (heparin 0.4 U. kg$^{-1}$ min$^{-1}$) in random orderseparated by 60 min washout periods. The rise in fatty acid substrate was similar for each infusion. The ketogenic index (KI)-the ratio of integrated ketone body to fatty acid concentrations-for E (1.1 ± 0.1) and for NE (1.1 ± 0.1), was significantly higher (P<0.01) than for the fatty acid control (0.3 ± 0.1). **Pathophysiological protocol**: Eight subjects received E (60 ng.kg$^{-1}$ min$^{-1}$), NE (80 ng.kg$^{-1}$ min$^{-1}$), and control infusions. Despite higher fatty acid levels, the integrated ketone body response for E was lower than that observed in the physiological protocol (26.6 ± 4.2 vs 44.3 ± 5.3 mM.min, p<0.05). The KI for NE (0.7 ± 0.1) was significantly higher (p<0.01 ) than for either E (0.3 ± 0.1) or the fatty acid control (0.2 ± 0.1). Significant (p<0.01) elevations were observed in glucose and insulin levels during E infusion in the latter protocol. These results indicate comparable direct ketogenic effects of E and NE at low physiological plasma concentrations in normal man. In contrast, at pathophysiological plasma levels, NE exerts additional ketogenic effects, whereas E has a relatively antiketogenic action in concert with elevations of plasma glucose and insulin concentrations.

## Insulin resistance syndrome underlies high prevalence of NIDDM in South Asians but not in Blacks.

*PM McKeigue, MG Marmot,*
*London, UK.*

South Asians and Blacks have higher prevalence of NIDDM than Whites. We compared glucose tolerance, body fat pattern and cardiovascular risk factors in these groups in a population survey of 3143 men aged 40-64. Diabetes prevalence was 5% in Whites, 19% in South Asians and 15% in Blacks (Black/White odds ratio 3,5, 95% CI 2.4-5.3). Diabetic and IGT men were grouped as glucose intolerant (GI) and compared with normoglycemics (NG) in each group:

| | White | | S. Asian | | Black | |
|---|---|---|---|---|---|---|
| | NG | GI | NG | GI | NG | GI |
| N | 1392 | 118 | 1062 | 362 | 159 | 50 |
| 2-h insulin (mU/L) | 19γ48 | | 38 γ 70 | | 20 γ46 | |
| Waist-hip ratio | 0.93γ0.99 | | 0.97γ1.00 | | 0.93γ0.98 | |
| Systolic BP (mmHg) | 121γ132 | | 124 γ132 | | 125α135 | |
| Triglyceride(mM) | 1.37γ2.13 | | 1.68 γ2.14 | | 0.98β1.39 | |
| HDL chol (mM) | 1.27γ1.17 | | 119 γ1.15 | | 1.35 γ1.31 | |

(α=p<0.05, β=p<0.01, γ=p<0.001)

A syndrome of hyperinsulinemia, central obesity, hypertension, high plasma triglyceride and low HDL cholesterol is present even in normoglycemic South Asians but not in normoglycemic Blacks. Insulin resistance may account for high diabetes prevalence in South Asians but not 8lacks; this may be relevant to ethnic differences in cardiovascular risk.

### Glucose Uptake to Insulin and Glucokinase Activity of Skeletal Muscle from Various Type of Obesity

*M. Umahara, K. Ohshima*, S. Okada. T Onai, M. Satoh, Y. Nakamura and I. Kobayashi Gunma, Japan.*

A comparisons has been made on the insulin resistance of skeletal muscle among various type of obesity, using the perfused hindquarter preparation. We measured glucose uptake (GU:nmol/min./g. tissue) or 2 deoxy glucose phosphate accumulation (2GDPAlnmol/l5min./g.tissue) in ob/ob mice, gold thioglucose (GTG) induced obese mice and medial basal hypothalamic deafferentated (DEAFF) obese rats, in the basal (OmU/ml) and insulin stimulated (1 mU/ml) state. Also glucokinase activities (GKA:NADPH production rate, mmol/min./mg protein) were measured. Results are in below (*: $p < 0.05$).

| | OmU/ml | ImU/ml | GKA |
|---|---|---|---|
| ob/ob mice (2DGP-A) | 41.1* | 93.5* | 5.4 |
| Lean mice (2DGP-A) | 61.7 | 210.9 | 5.2 |
| GTG mice (2DGP-A) | 6.3* | 9.7* | 5.2 |
| Lean mice (2DGP-A) | 10.3 | 19.9 | 5.0 |
| DEAFF rats (GU) | 111.0 | 190.6* | |
| Lean rats (GU) | 109.1 | 336.1 | |

2DGP accumulation in ob/ob mice and GTG obese mice were significantly lower in both basal and insulin stimulated state than lean mice. But the GKA of both obese mice was not differ from lean mice. On the other hand in DEAFF rats, decreased glucose uptake was not observed in basal state.

The results indicate that reduced glucose transport activity plays a major role in the insulin resistance of the skeletal muscle in ob/ob and GTG induced obese mice. But the same can not be said in the state of insulin resistance in DEAFF rats.

## EPIDEMIOLOGY

### Prevalence of Diabetes Mellitus in rural Indian populations: Indian Council of Medical Research study, 1989.

*M.M.S. Ahuja and P.V Rao*
*All India Institute of Medical Sciences, New Delhi.*

Rural populations from North (male 596, female 662), South (male 1383, female 1616), West (male 1490, female 1209) and Eastern (male 1325, female 1669) regions of India, were screened for diabetes in 1989. All subjects, with two-hour capillary whole blood glucose after 75gm oral glucose as measured in reflectance meter exceeding 139 mg/dl, were retested for both fasting and two-hour blood glucose and diagnosed as per WHO criteria.

Out of these 9950 persons above 15 years of age, the overall crude prevalence of diabetes mellitus (DM) was 0.48% in North, 2.43 % in South, 1.93% in West and 0.43% in East, and the previously diagnosed cases were 56.9% of the total diabetics ascertained. Impaired glucose tolerance was noted in 0.32%, 0.20%, 0.30% and 0.33% in these populations respectively. Age in years (normal vs. DM=male, 36.0 ± 16.5 vs. 48.9 ± 14.2 p<.001; female, 35.5 ± 15.6 vs. 53.9 ± 13.2 p<.001), and body mass index ($Wt/Ht^2$) (normal vs. DM = male, 19.1 ± 2.9 vs. 20.9 ± 3.8 p<.001; female, 19.1. ± 3.0 vs. 22.7 ± 4.7 p<.001) were the important risk variables positively associated with DM in these rural Indian populations.

### Diabetes Mellitus in population living at high altitudes in Himalayas

*S. S. Kaushal, P. V Rao, A. Bharadwaj, I.M.S. Lamba, D.J. Dasgupta, A. Anand and M.M.S. Ahuja*
*All India Institute of Medical Sciences, New Delhi.*

A total of 999 subjects (432 male, 567 female) were screened for diabetes mellitus (DM) out of 1203 persons of Indo-Chinese origin above 15 years of age, in Chini village situated in the Himalayas at an altitude of 2759 meters. All subjects, with two-hour capillary whole blood glucose after 75 gm oral glucose as measured in reflectance meter exceeding 139 mg/dl, were retested for both fasting and two-hour blood glucose and diagnosed as per WHO criteria.

The overall crude prevalence of DM at 0.4% (0.7% male, 0.2% female) was the lowest reported in Indian populations, and half of them were already on specific therapy. Prevalence of impaired glucose tolerance in this population was 1.0% (0.2% male, 1.6% female). On regression analysis, it was noted that DM was positively associated with the age of an individual (p<.01 in both sexes), and the body mass index ($Wt/Ht^2$) (p<.01 in females, p<.05 in males). As evidence for DM in parents was significant in diabetic men (p<.001) and not in women, inheritance seems to be an important risk variable for DM in men in this population.

### Profile of childhood diabetes mellitus in India: regional, ethnic and social variations. Research society for study of diabetes in India

*Prepared by A. Virmani. Investigators: PSN. Menon, KC. Samal, S. Venkataraman, V Mohan, A. Abraham, New Delhi. India*

| Center/ Region | n % | IDDM % | FCPD % | NIDDM | Onset DM:yr |
|---|---|---|---|---|---|
| Delhi/north (Pu) | 168 | 99 | 0.5 | 0.5 | <20 |
| Cuttack/east (Pu) | 90 | 88 | 12 | 0 | <15 |
| Madras A/South (Pu) | 160 | 95 | 4 | 1 | <20 |
| Madras B/South (Pv) | 252 | 67 | 11 | 22 | <20 |
| Cochin/South (Pv) | 58 | 67 | 19 | 14 | <20 |

Service: Pu=public; Pv=private (fee for service)

As in the rest of the world, IDDM is the pre-dominant form of childhood onset diabetes all over India, and almost exclusively so in north India (Aryan descent). Childhood onset FCPD (tibrocalculous pancreatic diabetes; non-alcohol) was prevalent in south and east India, especially the southmost state of Kerala (Cochin). Childhood onset NIDDM was observed in south India (Dravidian descent), in

private institutions (Madras B and Cochin) serving the higher economic strata (also observed in Indian migrants to South Africa). Three centers (Cuttack, Madras A and Madras B) designated 28, 17% and 2% respectively of the 'IDDM' subjects to 'Protein Deficiency Diabetes Mellitus' group (WHO).

## CLINICAL FEATURES

### Evaluation of Linear growth in prepubertal Insulin-dependent diabetics

*H.B. Chandalia and T Sahastrabudhe*
*Bombay, India.*

Height-centiles, as determined from the tables compiled by Indian Council of Medical Research, were calculated in 89 insulin- dependent diabetics (IDDs) with onset of diabetes in the pre-pubertal period. Percent of IDDs in each height-centile group were as follows: 15.73% (0-10 centile), 28.08% (11-25 centile), 17.97% (26-50 centile), 15.73% (51-75 centile), 10.11% (76-90 centile), 12.36% (91-100 centile). Seventeen of these patients were at the prepubertal stage. Their height-velocity, as calculated from a minimum follow-up of 6 months in every patient was (Mean ± SD) 5.67 ± 1.9 cms per year.

Bone age was evaluated by Tanner-Whitehouse (TW-2, RUS) method in 11 IDDs. Chronological age and bone-age (Mean ± SEM) in this group was 9.09 ± 1.27 and 9.40 ± 1.47 years respectively. All of these patients were on two-dose insulin therapy. The glycated Hb (Mean ± SEM, n=51 ) was 9.84 ± 0.3% in this group. Taking glycated Hb of <8%, 8-10%, and >10% as indicative of good, fair and poor control respectively, these diabetics were under fair metabolic control.

We conclude that normal linear growth can be achieved in pre-pubertal IDDs with fair control of diabetes.

### Ten-Year Follow-up Study of Overweight Subjects with Normal or Impaired Glucose Tolerance: Can We Predict the Development of Diabetes?

*Y. Nagasawa. T Yamada, M. Ishihara, M. Komatsu, L. Komya, T Shinoda and T. Aizawa*
*Matsumoto, Japan.*

Sixty-three overweight (BMI≥26) subjects (41-72 yrs, 14 men and 49 women) with normal or impaired glucose tolerance (NGT or IGT, respectively), as judged by 75 g OGTT, were followed for 10 years. The patients were classified into 4 groups based on the follow-up results: those with NGT remained NGT (NN n=9), NGT progressed to IGT (Ni+n=4), IGT remained IGT or reverted to NGT (Ii+N, n = 34) and IGT developed diabetes $I_D$, n=16). None of NGT subjects developed diabetes. To identify the predictor of later development of diabetes, the initial age, BMI, IRI, Plasma glucose (PG), $\Delta PG/\Delta IRI_{30\ min}$ and the family history of diabetes were compared among the groups. $N_N$ and $N_I$ groups were indistinguishable by all means. The fasting and peak PG, Σ PG $\Delta PG/\Delta IRI_{30\ min}$ and BMI were significantly greater and the prevalence of diabetes in the family was significantly higher respectively, in lo than in $I_{I+N}$ groups, the 2 groups were similar in other respects. Among IGT patients, 11 of 14 (79%) with ΣPG ≥700 mg/100 ml or positive family history developed diabetes and only 1 of 32 (3%) with Σ PG < 700 and negative family history developed it. Glucose tolerance little worsened in $I_{I+N}$ during the 10 years and the progression of IGT to diabetes accompanied reduction and delay of insulin secretion.

Overweight adults with IGT are dichotomic: those with Σ PG> 700 or positive family history are diabetes-prone whereas those with Σ PG < 700 and negative family history are diabetes-resistant.

## MONITORING CONTROL

### Hair glycation for evaluating the time and pattern of onset of diabetes

*Shogo Masuta, Horoyuki Shoda, Hiroyuki Yamada, Makoto Sakai, Naoya Igaki, Kunihiro Doi, Munetada Oimomi, and Masato Kasuga Kobe, Japan.*

Furosine derived from fructose-lysine, which was formed by binding of lysine residue of hair protein, was measured and used as an indicator of glycation. We have reported that the past blood glucose level at arbitary time can be estimated from hair glycation by considering the rate of hair growth and the distance of hair from the scalp. In the present study, taking the advantage of the characteristic that hair is continuous, we estimated the time of onset of diabetes by measuring hair glycation in 25 patients with apparently acute onset of diabetes. Furthermore, we classified the pattern of onset of diabetes and investigated the respective patterns of onset.

Hair was cut in every 0.5 cm length from the scalp. After acid hydrolysis of hair samples (about 50mg), furosine was measured HPLC using a ODS-120A column, 7mM H3P04 as a solvent and UV detector wavelength, 280nm. The level of furosine was expressed as the ratio of the area under the furosine peak to that under the tyrosine peak.

We classified the pattern of onset of diabetes into the following three types according to the ascending gradient of hair furosine levels at the time of onset of diabetes; acute onset type-the blood glucose level was rapidly elevated from normal level within one month; gradual onset type-elevation of blood glucose level occurred gradually; and previous onset type-diabetes has been present. Survey of therapeutic modalities given at least 6 months after onset, by type of onset, showed that 78% of patients belonging to acute onset type were receiving insulin, while 82% of patients belonging to previous onset type could be treated without insulin.

Thus, measurement of hair glycation in patients who appear to have developed diabetes acutely may allow us to predict future diabetic treatment from the pattern of onset of diabetes in the early stage of diabetes.

### Evaluation of serial Fructosamine assays as an Index of Diabetic Control

*N.P.S. Verma, P. Sabharwal, A. Goel. M.K. Bhatnagar, U.P.S. Chauhan*
*Dr. Ram Manohar Lohia Hospital, New Delhi, India.*

Fructosamine has been proposed as a useful intermediate measure of diabetic control. Serial fructosamine estimations were performed in 30 uncontrolled diabetics and 10 healthy controls to evaluate its utility in ascertaining the diabetic control. Assay was performed at the entry to the study and at

weekly intervals thereafter for a period of 4 weeks. Mean pre-study fructosamine value in diabetics (3.07±1.04 mM) was higher when compared to controls (1.09±0.26 mM) and correlated significantly with mean pre-study fasting venous blood glucose value (r = 0.89 and 0.92 respectively). Fructosamine values were independent of related biochemical parameters like albumin, lipoproteins and urea.

With institution of treatment, mean fructosamine value declined progressively from 3.07 mM to 1 .80 mM at the end of the fourth week. This paralleled a decline in mean fasting venous blood glucose level from 236.30±86.74 to 120.18±31.16 mg/dl. This decline was independent of the type of diabetes and treatment modality utilized.

Serial fructosamine assays performed at weekly intervals are an effective measure of the control achieved in the diabetic individual.

## A New Semi-quantitative Dip-stick for Micro-albuminuria

*H.J. Bangstand, K Try, K. Dahl Jorgensen, K.F. Hanssen*
*Oslo Norway.*

Microalbuminuria is a predictor for later clinical diabetic nephropathy in both insulin-dependent and non-insulin dependent diabetes mellitus and for increased cardiovascular mortality. Elevated urinary albumin excretion is potentially reversible when near-normoglycemia or lowering of blood pressure are obtained. So far only qualitative methods have been available for screening in the low microalbuminuric range. We have compared a new side- roorn, semi-quantitative dip-stick test (Micral-test) with a quantitative immunoturbidmetric method. Overnight urines from 203 diabetics were consecutively tested. 186 samples contained <200 mg/I albumin and were subsequently analysed.

We found a correlation coefficient of 0.82 between the new semiquantitative method and the reference method. Elevated albumin concentration was defined as > 20 mg/I albumin in overnight urine and the prevalence of samples with values above this levels was 28.0%. Using this definition the Micral-Test areas of 20 mg/I or above had a sensitivity of 92.3%, a specificity of 82.1%, a negative prediction value of 96.5% and a positive prediction value of 66.7%. 84.9% of the diabetics were correctly classified as either having elevated urinary albumin concentration or not.

Our conclusion is that the Micral-test is useful in screening for elevated urinary albumin concentration and for monitoring the development of urinary albumin excretion in the low microalbuminuric range.

## Monitoring the electrocardiogram could be an easily detectable marker for hypoglycemia

*W. Kunze and L. Heinemann*
*Dusseldorf, Germany.*

Looking whether the changes in the electrocardiogram (ECG) during subnormal and hypoglycemic blood glucose concentrations are of such a magnitude that they could be analysed by a small, portable computer and whether the changes are influenced by the quality of metabolic control, we measured ECG in 6 type-I (insulin dependent) diabetic patients in good metabolic control (GDiab) ( mean HbAlc (SD) 6.4 (0.5)%) and 8 patients with moderate metabolic control (MDiab) (8.7(0.8)%), where blood glucose concentrations (BG) were lowered stepwise and clamped for 45 min each at 5.0, 3.6, and 2.5 mmol/l and than returned to basal values. From standard ECG registrations under rest conditions the amplitude of the R-wave and the T-wave were measured and the ratio R/T calculated.

Changes in percent against baseline values at 5.6 mmol/I (GDiab) and 11.1 mmol/l (MDiab) are given. Whereby the amplitude of the R-wave remains nearly constant at all BG, the amplitude of the T-wave changed, so the R/T ratio in GDiab increased from zero to 10.0 (3.4)% (mean (SD)) at 5.0 mmol/l ($p<0.01$), to 24.6 (18.1) at 3.6 mmol/l ($p<0.01$ ), to 44.3 (28.3)% at 2.5 mmol/l ($p<0.001$ ) and returned to 10.4 (27.0)% at baseline (NS). No significant differences between GDiab and MDiab were found at baseline, at 2.5 mmol/l and after returning at baseline, but at 5.0 mmol/l and at 3.6 mmol/l ($p<0.02$).

These preliminary results indicate that probably by analysis of surface ECG by a small computer a lowering of BG to hypoglycemic values could be detected; especially in BG monitoring during the night.

## Recovery of Used Reagent Strips: A Useful and Inexpensive Step for a Quality Control (QC) Program for Hospital Use of Glucose Meters

*C. Nardolillo and J.F. Yale*, Montreal*
*QC, Canada.*

Glucose meters and increasingly used for in-hospital measurements of blood glucose. As apart of our QC program, we assessed the effects of inadequate blood coverage of the strip reagent pads on the glucose results obtained, and evaluated the frequency of this type of error in our hospital.

Using maleimide-stabilized blood, we compared the results obtained with an adequate full coverage of the reagent pads (control values) to those obtained with incomplete blood coverage (A: ■ B:◘ C:□ D: ◙) using 5 reflectometers (Accu-Check II, Glucometer II, One Touch, Glucoscan 3000 Tracer) (n= 20/pattern/meter). The results were 98±1% of the control value for the A pattern, 65±2% for B, 52±4% for C and 48±3% for D.

We collected all strips used in the hospital (one brand of meters) and assessed their coverage with blood by dividing the reagent pads into 9 squares and assessing the area with color changes. Of the 12939 strips assessed from 34 wards, 57.2% had complete blood coverage and 27% had an adequate coverage, missing only one or more corners (pattern A). Inadequate coverage corresponding to patterns B, C and D occured in 3.4%, 2.5% and 0.5% of the strips, respectively, while 8.8% of the strips had other patterns of inadequate coverage. The centre was inadequately covered in 0.6% of strips.

### Conclusions:

1) Indequate blood coverage of the strip reagent pads can lead to clinically significant errors in glucose measurement. 2) This error is frequent during in-hospital use, and 3) the collection of used strips is a simple and inexpensive measure to screen for this error.

## TREATMENT-INSULIN THERAPY

### An Insulin Infusion Algorithm to Achieve and Maintain Overnight Normoglycemia

*J. Gerich, and M. Mokan*
*Pittsburgh, PA.*

We describe here nursing staff use of an insulin infusion algorithm to achieve and maintain overnight normoglycemia in type I and type II diabetes.

| Infusate Insulin Concentration (U/I) | Patient Wt. (Kg) | Plasma Glucose (mg/dl) | Insulin Infusion Rate (CC/hour) |
|---|---|---|---|
| 80 | 60-65 | < 95 | 0 |
| 88 | 66-70 | 100-119 | 5 |
| 96 | 71-75 | 120-139 | 10 |
| 102 | 76-80 | 140-159 | 15 |
| 112 | 81-85 | 160-179 | 20 |
| 124 | 86-90 | 180-240 | 40 |
| 140 | >90 | >240 | 60 |

Insulin infusions were begun at 9 p.m. in 20 hyperglycemic (249± 21 mg/dl) diabetic volunteers withdrawn from their depot insulin. Infusion rates were adjusted at 30 min intervals according to the above algorithm based on half hourly plasma glucose determinations. Nearnormoglycemia was established by 2:30 a.m. (113 ± 7 mg/dl). Plasma glucose averaged 113± 3 mg/dl between 2:30 and 7:30 a.m. (CV 9 ± 1%). The average insulin infusion rate was 0.01 U/min (0.13 mU/kg/min). The lowest plasma glucose was 83 mg/dl and the highest was 175 mg/dl. No patient required glucose administration. We conclude that it is possible for nursing staff to safely establish and maintain near normoglycemia overnight in diabetic patients with use of an insulin infusion algorithm.

### Clinical Trial of a New Nasal Insulin Preparation

*RR Holman, J Steemson*
*Oxford, U.K.*

Novolin Nasal U200, a recently developed nasal insulin preparation using phospholipid as an absorption enhancer and designed to be delivered as a nasal spray, has been successfully tested in volunteers.

Ten IDDM patients have now completed a double blind randomised trial comparing the glycaemic response to single doses of soluble insulin administered subcutaneously 30 minutes before a standard breakfast and an equivalent dose given as an intranasal spray with the meal. Each patient was studied on six occasions, three times on each therapy, taking their normal basal insulin injection on the preceding day. Regular blood samples were taken for six hours after the meal with no snack being given.

No problems were experienced with the nasal insulin preparation apart from transient minor nasal irritation in two patients. All patients felt the preparation would be acceptable for long term therapy. Four hypoglycaemic episodes occurred after subcutaneous and one following nasal insulin adminstration.

Plasma insulin levels peaked rapidly and with less variation after nasal (mean 35, range 20-50 minutes) than after subcutaneos insulin (mean 94, range 30-270 minutes). Insulin levels returned to baseline by 90 minutes following nasal insulin but extended to > 300 minutes with subcutaneous insulin in most patients. The incremental plasma insulin rise was significantly greater with nasal insulin adminsitration (mean 30.2 v 14.5 mU/l, $p < 0.001$) but there were no differences in the mean incremental plasma insulin or glucose areas.

Nasal insulin appears to provide a more predictable and physiological plasma insulin profile than subcutaneously administered insulin.

### Is Insulin important in the Perception of and Cognitive response to Hypoglycemia in patients with Insulin Dependent Diabetes (IDDM)

*D. Kerr, M. Reza and BA. Leatherdale*
*Southampton, England.*

Many patients feel and appear "normal" despite hypoglycemia, suggesting that individuals can adapt to a low blood glucose. This study examined whether insulin modifies the subjective and cognitive responses to hypoglycemia.

9 patients with IDDM participated in 3 hyperinsulinemic glucose clamps in a random order. After 60 min at 81 mg/dl blood glucose was (a) clamped at 81 mg/dl for 240 min (euglycemic study), (b) lowered to 50 mg/dl for 180 min followed by 60 min at 36 mg/dl, using an insulin infusion rate of 40 $mU/m^2$/.min and (c) as (b) but using an insulin intusion rate of 120 $mU/m^2$/min. Symptoms and awareness of hypoglycemia (100 mm visual analogue scales) and cognitive function (semantic processing, Weschlar digit symbol substitution and grooved peg-board tests) were assessed every 30 min.

There were no subjective or cognitive changes during the euglycemic study. Subjects were less aware and had fewer symptoms of hypoglycemia during the higher (120 $mU/m^2$/min) insulin infusion rate ($p<0.01$). All 3 tests of cognition showed significant impairment after 60 min of hypoglycemia ($p<0.001$) but thereafter did not change with time, or insulin level. Cognitive impairment was however more marked when blood glucose was lowered to 36 mg/dl compared to 50 mg/dl ($p<0.01$).

We conclude that the prevailing insulin level influences the perception of and symptomatic responses to hypoglycemia. Cognitive impairment is dependent on depth rather than duration of hypoglycemia.

### Delaying Meal Times Following Insulin Injection-Is it necessary?

*J. Alford, S Twigs, L. Molyneaux, S. Mclennan, M. Mcgill, D. Yue, J. Turtle*
*Syndey, Australia.*

This study was designed to establish the effect of differing insulin injection times or i) post-prandial rise in blood glucose levels and ii) diabetic control.

10 NIDDM patients (duration 13.5±8.1 years; weight 79±14 kgs; HbAIC 8.3±1.4%) on twice daily mixed insulins were assigned to receive theirshort acting insulin, in random order, 0, 30, or 60 minutes preprandially, each for a three week period. The timing of the long acting insulin remained at 30 minutes throughout the nine weeks of the study. Patients were asked to measure BSL's pre and two hours post

breakfast and the evening meal. Fructosamine was measured at baseline and at the completion of each three week period. A standard breakfast was also given after each three week period and BSL's were measured fasting and at one, two and three hours postprandially.

| BASAL | 0 min | 30 min | 60 min |
|---|---|---|---|
| **Fructosamine (mM)** | | | |
| 3.5 ± 1.2 | 3.3 ± 1.1 | 3.5 ± 1.3 | 3.1 ± 0.8* |
| **Home Blood Glucose Monitoring (mM)** | | | |
| Preprandial | 10.8±2.6 | 10.5±2.5 | 9.1±2.4* |
| Postprandial | 11.6±3.0 | 11.0±3.5 | 9.9±3.3# |
| **Standard Breakfast-BSL (mM)** | | | |
| Preprandial | 10.2±4.5 | 10.8±2.7 | 10.2±5.6 |
| Postprandial rise | 15.2±10.6 | 15.6±8.6 | 14.9±6.4 |

$p < 0.05$: *vs all time points, # vs O min, ANOVA

We conclude that postprandial rise in blood glucose is independent of whether the short insulin is given 0, 30 or 60 minutes before hand. However, taking short acting insulin 60 minutes prior to meal times leads to better diabetic control by lowering preprandial blox glucose level.

## Hypoinsulinemia is Not Critical to Glucose Recovery from Hypoglycemia in Humans

*Simon R, Heller and Philip E Cryer*
*St. Louis, MO, USA.*

To test the hypothesis that glucose recovery from hypoglycemia can occur in the absence of hypoinsulinemia, we studied 9 normal humans on 6 occasion in random sequence: 1) Control: Saline 0- 240 min. 2-6) Experimental: Insulin 0.6 mU $kg^{-1}.min^{-1}$. 0-80 min., then 0.0, 0.1, 0.2, 0.4 or 0.6mU. $kg^{-1}.min.^{-1}$ 80-180 min. In the experimental studies, plasma glucose (PG) plateaued at -3.3 mmol/.L despite -6-fold and -3-fold elevations of peripheral (Pe) and calculated hepatic portal (Po) insulin levels respectively. In the recovery period (80-180 min.) glycemic steady states were achieved at 140-180 min. -4-fold Pe with -2-fold Po insulin elevations prevented glucose recovery (PG=3.6 ± 0.1 mmol/L). However, biological glucose recovery (increments in PG to 4.3± 0.1 mmol/L with decrements in glucagon, epinephrine, growth hormone and cortisol to control values) occurred despite Pe hyperinsulinemia (54 ± 4 vs. 32 ± 4 pmol/L, P< 0.01) in the absence of Po hypoinsulinemia (58 ± 4 vs. 68 ± 8 pmol/L). Thus, we conclude that in normal humans: 1) Glucose counterregulatory systems prevent severe hypoglycemia despite substantial hyperinsulinemia. 2) Dissipation of insulin normally plays an important role in the correction of hypoglycemia. 3) Biological glucose recovery, to plasma glucose levels above the thresholds for activation of counterregulatory systems (-3.8 mmol/L) and well above the thresholds for symptoms of hypoglycemia (-2.9 mmol/L), can occur in the absence of portal hypoinsulinemia and despite mild peripheral hyperinsulemia.

# TREATMENT-ORAL HYPOGLYCEMIC AGENTS

## The Effectiveness of the Combined Therapy of Sulfonylurea (SU)/Insulin in NIDDM

*Mitsuaki Kodama, Hiroshi Nakahra, Masaru Usami, Masaki Ikeda Hyogo, Japan.*

We have demonstrated the effectiveness of the combined therapy of SU/insulin in NIDDM. The following cases were included (I) secondary failure to SU agents, (II) insulin doses are excessively required, (III) cases with remarkable elevation of post-prandial blood glucose, (IV) old-aged diabetics with unstable glycemic controls by insulin. In group A, they were added insulin to SU (n = 46, average age: 57, duration: 13.7 years). Chlorpropamide and glibenciamide were mostly used. The dose of insulin added to SU agents was initially 8.4 and increased 13.9U two years later. FBS and HbAlc drastically improved 3 months later from 217 to 141 mg/dl, from 9.7 to 7.7%, respectively. After 6, 12, 24 months, both FBS and HbAlc values slightly increased, but still sustained lower levels in the 24 months comparing with before the combination therapy. In group B, they were added SU to insulin therapy (n= 45, average age: 61, duration: 13.7). The dose of insulin before combined therapy was 22.5U, and it increased 24.2U 2 and 3 years later. 3 months after combination therapy, averaged values of both FBS and HbAlc improved from 192 to 132mg/dl, from 9.4 to 7.4% with an elevation in C-peptide responses to meal. In most NIDDM, the efficacy of the combined therapy was clear in 3 and 6 months. On the other hand, the effect of long term was not evident. These phenomena may be due to decrease of C-peptide reaction and possibly the down sensitivity of insulin as time goes on. However, we must evaluate the results concerning with various factors in clinical practice of diabetics.

## Effect of Oral α-Glucosidase Inhibitor BAY g5421 on Glucose Uptake in Skeletal Muscle

*J.C. Young*, T.G. Kurowski, T. O'Hare, J.R. Vasselli*, and N.B. Ruderman**
*Boston, MA.*

The oral α-glucosidase inhibitor BAY g5421 (acarbose) is effective in dampening postprandial glucose and insulin excursions in rats fed a high carbohydrate diet. Acarbose acts by inhibiting several small intestine oligosaccharidases slowing carbohydrate absorption. Recent evidence suggests that acarbose may secondarily enhance peripheral insulin sensitivity. The purpose of this study was to evaluate the effects of acarbose on insulin-stimulated glucose uptake in skeletal muscle. Female Sprague-Dawley rats (230-270g) were fed either (A) a control diet (Purina chow); (B) a high CHO diet (CHO 62, fat 26, protein 14%); or a high CHO diet plus acarbose [(C) 10 mg/100g food or (D) 20 mg/100 food], for 9 wks. Weight gained (g) was: (A) 38 ± 4*, (B) 78 ± 5, (C) 64± 5, (D) 54± 8* (*p<0.05 vs B). Glucose uptake in skeletal muscle was determined using the perfused hindlimb preparation. In the presence of 500 μU/ml insulin, glucose uptake was reduced by 50% in the high CHO group (B) relative to the controls (A). Acarbose (20mg/100g food) reversed peripheral insulin resistance caused by high CHO feeding. Glucose uptake (μmol/g/hr) was: (A) 9.7± 1.8*; (B) 5.0 ± 0.4; (C) 6.1 ± 0.7; (D) 7.0± 0.5* (*P<0.05 vs B). To elucidate a mechanism for the peripheral effect of acarbose, insulin receptor binding and tyrosine kinase activity were determined in pooled soleus, red gastrocnemius, and red

quadriceps muscles taken following hindlimb perfusion. Insulin receptor binding did not differ between the 4 groups. Basal and insulin stimulated autophosphorylation of WGA-purified insulin receptors was comparable between the 4 groups, as was phosphorylation of exogenous substrate. These results indicate that acarbose acts indirectly on skeletal muscle to attenuate dietary-induced insulin resistance. They also suggest that the site of action for this effect is located at a point distal to the insulin receptor.

## Hypoglycemia unawarness among Non-Insulin Dependant Diabetics (NIDDM) Treated with sulphonylureas

*Pradeep G. Talwalkar*
*India.*

The specific problems of diabetics on insulin who are unaware of hypoglycemia are known. There is a paucity of similar data in NIDDM patients on Sulphonylureas. Hence it was decided to analyse data of 21 successive NIDDM patients on Sulphonylureas requiring emergency hospitalisation with special reference to hypoglycemia un-awareness. Twenty-one patients (age 51-80 yrs.) were studied. 15 were aged 65 & above. Duration of diabetes ranged from 2-25 yrs. (Mean 7.2 yrs). Random blood glucose values on admission ranged from 1.51 to 3.13 mmol/L. Table I shows Sulphonylureas involved and its dosage.

Table I

| Drug | Mean Daily Dosage | No. of Patients |
|---|---|---|
| Glibenclamide | 5.50 | 10 |
| Chlorpropamide | 325.00 | 6 |
| Glioizide | 5.00 | 4 |
| Tolbutamide | 250.00 | 1 |

A striking feature was absence of any significant adrenergic symptom in 19 out of 21 patients. In 10 of these 19 patients, clinical features suggestive of autonomic neuropathy were present. Detailed study of precipitating & predisposing factors was done. Hypoglycemia requiring emergency hospitalisation is more common in older diabetics on Sulphonylureas & often the patients are unaware of it, probably because of associated autonomic neuropathy. Large scale edu. programmes is the need of the day.

## Effects of gliclazide on platelet reactivity and free radicals in type 2 diabetic patients: clinical assessment

*P.E. Jennings, N. Scott, A. Saniabadi and J.J.F Belch, Department of Medicine, Ninewells Hospital, Dundee, DD 19SY Scotland.*

Our in-vitro studies have demonstrated that Gliclazide has free radical scavenging and anti-platelet activities. To assess this clinically we studied Gliclazide in a blinded randomised Glibenclamide controlled trial in 30 type 2 diabetic patients with retinopathy. All patients had been taking Glibenclamide for over 12 months before being randomised to receive either an equipotent dose of Gliclazide (Grp A) or continue on Glibenclamide (Grp B) but diabetic control was not modified. The patients were well rnatched at randomisation (mean age 58 yr, duration of diabetes 8 yr, 20 male, mean HbA1 % 8.6 %) and the diabetic control did not alter during the trial. Free radical activity was assessed as oxidative status by plasma thiols (PSH), lipid peroxides (MDA-LM) and red cell superoxide dismutase activity (SOD). Platelet aggregation in whole blood to collagen (Plt-ag) was used as the measure of platelet reactivity. There were no differences between these measurements at baseline. At 3 months the oxidative status and platelet aggregation in the Gliclazide group (Grp A) had improved significantly compared to baseline and had also showed significant differences in all parameters when compared to Grp B. Therefore, comparing Grp A to Grp B: PSH 458.5 ± 9.8 v 415.5 ± 5.14 µmol/Lp<0.02, MDA-LM 7.05 ± 1.12 v 8.25 ± 0.41 µmol/l, p<0.03; SOD 93.8± 9.6 v 123± 5 µg/mL, p<0.02; Plt-ag 71.0± 3.8v. 47.5 ± 5.4%, p<0.003. These results confirm in a clinical study that Gliclazide is a powerful general free radical scavenger. The effects on platelets may be secondary to this as it appears to be independent of diabetic control.

## M16209: A Novel Hypoglycemic Agent Possessing Aldose Reducatse Inhibiting Activity.

*K. Kato. N. Murakami, Y. Yamaguchi, J. Ishiguro, I. Miwa* and J. Okuda*, Y. Hasegawa, K. Nakayarna, M. Ohta, M. Mrzota*
*Tokyo and Nagoya, Japan*

We have reported M16209 (1-(3-bromobenzo (b) furan-2-ylsulfonyl (hydantoin) is a potent inhibitor of aldose reductase and exhibits beneficial effects in animal models of diabetic neuropathy and sugar cataract. In the present studies, we focused on the hypoglycemic activities and mechanism of action of M16209. Oral administration of M16209 (100mg/kg) produced only small decrease in blood glucose levels in normal rats, but produced remarkable decrease in blood glucose levels in streptozotocin (STZ)-induced non-ketotic diabetic rats. M16209 was also effective in improving (iv) GTT in normal rats. Moreover, M16209 ameliorated impaired OGTT in NIDDM rats (neonatal STZ rats). M16209 elevated serum insulin levels in diabetic or glucose-loaded animals with hyperglycemia, while the compound had little effect on serum insulin levels in normoglycemic animals.

These results suggest that M16209 is a novel hypoglycemic agent without inducing hypoglycemia and that the potentiation of glucose induced insulin secretion is involved in the hypoglycemic mechanism of M16209. Therefore M16209 is expected to be a clinically useful antidiabetic drug possessing both hypoglycemic and aldose reductase inhibiting activity.

## A New Oral Hypoglycemic Agent, Pioglitazone, Improves Lipid Metabolism in Wistar Fatty Rats

*H. Ikeda, H. Odaka, N. Miki and T. Matsuo.*
*Takeda Chemical Ind., Osaka, Japan.*

Hyperlipidemia and the abnormal lipoprotein profile associated with NIDDM are closely related to the development of coronary heart disease and macroangiopathy. A new hypoglycemic agent, pioglitazone (PI, 5-[4-[2-(5-ethyl-2-pyridyl) ethoxy]benzyl]-2, 4-thiazolidinedione), increases insulin sensitivity in both in vitro and in vivo experiments. The aim of this work was to clarify the effect of

PI on lipid dysmetabolism in NIDDM. Male Wistar fatty rats (WFs) seem to be a good model for studying these aspects. They show many metabolic abnormalities: hyperglycemia; hyperinsulinemia; increased plasma triglyceride (TG), cholesterol (CH) and non-esterified fatty acids (NEFA); increases in small and large apo B moieties, apo C and apo E; increased hepatic TG secretion; and decreased TG clearance. Ten-week old WFs and their lean littermates (WLs) were given PI orally at a dose of 3 and 10 mg/kg/day respectively for 3 weeks. In WFs, PI normalized plasma glucose (Control vs PI: 361± 41 vs 132± 12 mg/dl) and TG (296±30 vs 84±7 mg/dl) levels; significantly lowered plasma insulin (435± 34 vs 284± 35 µU/ml), CH (106± 5 vs 90± 3 mg/dl) and NEFA levels; decreased apo B and C levels; and increased TG clearance (TI/2: 52± 11 vs 21± 3 min) without affecting the hepatic TG secretion rate and the postheparin plasma lipoprotein lipase activity. These effects were not prominent in WLS there findings suggest that insulin resistance is partially responsible for the abnormal lipid metabolism in NIDDM and that PI is efficacious in its treatment.

### Cost-effectiveness of Combined Therapy in Hispanic Non-Insulin- Dependent Diabetic Patients

*Mirza Martinez, Caguas*
*Puerto Rico.*

The medical records of ten medically-indigent Hispanic patients with NIDDM were studied to evaluate the cost-effectiveness of the combined use of insulin and sulfonylureas. Prior to the use of the combined regimen, the metabolic control of diabetes was considered poor: fasting plasma glucose levels (FPG) averaged 17.8 mmol/L (12.4-24.4). Many of the subjects were obese and had a history of poor compliance with diet. Six of the patients were using insulin; 4 used a second-generation sulfonylurea. Patients were asymptomatic, but all had some degree of macro-angiopathy. After one month of the combination regimen, the FPG decreased to 12.2 mmol/L (8.0-20.4) and at the three-month follow-up, the FPG averaged 12.4 mmol/L (8.1-22.6). The reduction in FPG was significant ($p<.05$) in the first month of therapy (5.6 mmol/L) and in the third (5.4 mmol/L). Nevertheless, good metabolic control (<7.8 mmol/L) was achieved in only 1 patient. At the three-month follow-up, 6 patients had FPG greater than 11 mmol/L. These findings may be related to poorly-controlled dietary habits, the degree of obesity, the educational level and motivation of the patients, as well as the possibility of noncompliance with the pharmacotherapy prescribed. Therefore, the clinical effectiveness of the use of insulin and sulfonylures remains controversial, especially in an environment that is not well controlled. If adequate metabolic control of diabetes is not obtained with the combined regimen, the cost-effectiveness analysis of the combination therapy does not warrant its use.

## TREATMENT-DIET

### Effects of a Diet Enriched in Monounsaturated Fat in NIDDM.

*J.G. Jimnez, H. Loenen, E. Mora-morales, M.A. Vargas*
*San Jose, Costa Rica.*

NIDDM patients commonly have dyslipidemia and are at high risk for coronary artery disease. To determine whether modify fat diets would improve glycemic control and lipid profile in NI DDM, we compared the effect of a standard diabetic diet (SD) with a diet enriched in maonounsaturated fat (ND) in eight NIDDM patients (Females: 6, Males: 2). Patients followed the SD (Kcal: 1116.8±146; CHO: 57.3±4.3%, total fat: 24.6±3.5%; saturated fat: 8.5±1.3%; monounsaturated fat: 10.1 ± 1.7%, polyunsaturated fat 6.0± 1,1%, p/S ratio 0.83± 0.2) for six weeks, followed by the MD (Kcal 111.1± 98.0; CHO: 52.8± 1.9%; total fat: 31.8± 1.4%; saturated fat: 8.5± 1.3%; monounsaturated fat: 17.3±0.8% ($p < 0.003$ as compared to SD); polyunsaturated fat: 6.2±0.7%; P/S ratio of 0.73±0.1, for another six week period. Body weight did not change during the two diets. Plasma glucose and lipid profile at baseline and at the end of each study period in females is shown in the table.

| mg/dl | baseline | end of SD | end of MD |
|---|---|---|---|
| Glucose | 182.2±24.6 | 128.1±5.3* | 133.3±7.9* |
| T. chol | 217.8±10.4 | 206.3±8.6* | 189.3±6.3* |
| Tg | 168.3±13.0 | 202.5±14.0 | 185.3±12.9 |
| LDL chol | 139.2±11.1 | 122.3±9.4* | 116.1±7.7* |
| HDL chol | 44.8±1.7 | 43.5±0.9 | 36.0±1.72* |

* $p < 0.05$ compared to baseline; * $p < 0.05$ compared to SD.

In males, glycemic and lipid control improved similarly. Despite HDL chol decreased, particularly at the end of MD, as a group, non-HDL chol changed from 174.1±8 to 166.0± 6.7 and to 155.5± 4.9 mg/dl during SD and MD, respectively ($p<0.05$). In conclusion, dietary enrichment with monounsaturated fat seems to induce beneficial effects on lipid profile and thus, may reduce coronary risk factors in NIDDM (X±SEM).

### Glycemic Response of Fruits in NIDDM

*A, Karol*, P. Kar*
*New Delhi, India.*

We studied glycemic responses to 15 commonly consumed Indian fruits in 44 NIDDM patients (Mean age 51.8± 7.1 yrs, mean % desirable body weight 115± 13 kgs, mean duration of disease 8.8 months, mean blood glucose-fasting 8.8± 1.6 mmol/1, post prandial 13.6± 1.3 mmol/1). Patients with acute stress, infection, nephropathy and blood glucose more than 16.8 mmol/l were excluded from the study. Each subject served as his own control and stopped antidiabetic drugs 1 week prior to the study. Glucose Tolerance Test (50gms) followed 2 days later by 'Fruit Tolerance Test' (in isocaloric exchanges) was performed and the glycemic and insulin response was observed in each patient. All fruits were well accepted by the patients except one who had nausea due large amount of water melon consumed. Glycemic Index (GI) for each fruit was calculated and on that basis fruits were classified as follows:

| | |
|---|---|
| <50% | Water melon |
| 50-60% | Apple, Melon, Orange, Papaya |
| 60-70% | Apricot, Guava, Pear, Pineapple |
| 70-80% | Apple & Orange juice, Sapota, Dates, Grapes, Lichi, Mango |
| >80 % | Banana |

Both whole apple and orange juice had lower GI than when given in juice form. GI was a direct function of carbohydrate and protein content ($p<0.01$) and was inversly related to the fibre content of the fruit ($p<.0001$). Positive correlation between GI and insulin response was also observed ($p<.01$). It is concluded that fruits with low GI can be consumed by diabetics. Whole fruit may be better than its juice form.

### Fish Oil versus Gemfibrozil in Hyperlipidemic Type 2 Diabetics

*P. Fasching, M. Rohac, K Ratheiser, and W. Waldhausl*
*Vienna, Austria*

To compare the impact of dietary fish oil supplementation (FO, 22 ml daily, containing 4.6 g of n-3 (omega-3) fatty acids, equalling 14.4 mmol) on carbohydrate and lipid metabolism vs. that of a conventional lipostatic therapy (Gemfibrozil (G), 900 mg daily, equalling 3.6 mmol) 9 hyperlipidemic Type 2 diabetics were included in a randomized short-time cross-over study. Duration of treatment was 2 weeks each, with an individual wash out period of 8 weeks. Lipid values were identical for both periods at baseline, and were reduced more markedly following G than after FO exposure (G/FO: Total cholesterol (chol), -13% **/-6%*; Total triglycerides (Tg), -39**/-18**; APOB, -17**/-10*; LDL-chol, -15**/0; VLDL-chol, -50**/-34**; VLDL-Tg, -44**/-27**). (p versus baseline: * < 0.05, ** < 0.01 ). Total-HDL, HDL2, HDL3 and APO A were not influenced by either G or FO. In parellel, no change by either G or FO was induced of intravenous glucose tolerance (1.2 mmol/kg bodyweight, t=30 min) and associated basal and incremental concentration of insulin and C-peptide. From this we conclude (1) that neither treatment affects carbohydrate metabolism in Type-2 diabetes and (2) that calculating the molar ratio (G/FO = 1/4) a greater hypolipidemic efficacy becomes apparent for G vs. FO.

## TREATMENT-EXERCISE

### Effect of Yogic Practices on the Exercise Tolerance in Diabetics

*B.K. Sahay, K.J.R. Murthy, P.S. Raju, KV.V. Prasad, and M.V. Reddy*
*Hyderabad, India.*

This study was carried out to evaluate the effect of yogic practices on the exercise tolerance in diabetics and in patients with diabetes and hypertension.

Seven diabetics (Group A) and 5 patients with diabetes and hypertension (Gr. B) have been investigated with reference to exercise tolerance while undergoing yogic practices. Graded submaximal exercise tolerance was studied in these patients in the beginning and after 8 weeks of yogic practices. The following parameters were studied in both groups before and after the graded exercise tolerance test: blood glucose, lactate, pyruvate and pyruvate lactate ratio.

The patients demonstrated a good control of blood glucose and blood pressure with reduction in drug requirements. Their exercise tolerance increased as noted by their ability to carry out exercise for longer periods. The lactate levels did not rise significantly after exercise at the end of the training period. The absence of increase in the blood lactate and the increase in their ability to perform exercise for longer periods indicate that their anaerobic threshold was postponed. Physical training exercise also improve exercise performance and postpone anaerobic threshold but yogic practices seem to do so without increasing oxygen consumption.

## TRANSPLANTATION & IMMUNOSUPPRESSION

### Successful Reversal of Type I Diabetes by a Bioartifical Pancreas

*P. Soon-shiong, R Heintz, N Merideth, E Feldman, R Nelson, G Skjak-break, O Smidsrod, T Espevik, M Otterlei,*
*Los Angeles, CA*

The technology of islet microencapsulation was described a decade ago. Significant advances toward clinical trials have been hampered by lack of successful large animal studies, as well as failure to identify mechanism(s) of fibrous overgrowth. We recently reported that mannuronic acid (M) plays an important role in the fibrosis associated with alginate-based microcapsules, Utilizing this knowledge, we explored the efficacy of microencapsulated islets in the treatment of Type I diabetes using a novel, low M alginate formulation. We report here the successful reversal of spontaneous Type I diabetes in dogs by the intraperitoneal implantation of microencapsulated islet allografts.

Eight spontaneous diabetic dogs entered the study with daily insulin requirements of 1 to 4 units/kg/day. Canine islets were prepared from pancreta of outbred mongrel dogs and transplanted intraperitoneally either as free islet controls (n=2), or as microencapsulated islets (n=6). In all 6 encapsulated islet recipients, euglycemia was achieved within 24 hrs with serum glucose falling from 364±106 to 97±32mg/dl. At the time of this report, 5 of the 6 recipients, ranging from 63 to 140 days post transplant, remain euglycemic, free of any insulin requirements. IVGTT performed pre and 14 days post-encapsulated islet transplant revealed K values of 0.59±5.1 and 3.0±0.74 respectively (n=6). The 2 recipients receiving free islets remained euglycemic for only 8 to 12 days despite average CSA blood levels > 200 ng/ml.

The is the first report of successful reversal of Type I diabetes by encapsulated islet transplantation in dogs. This study suggests that the glucose-insulin kinetics of the extravascular bioartificial pancreas are sufficient to achieve euglycemia in the large animal model and provides encouraging evidence of the feasibility of this technology for future clinical trials.

### Insulin indipendence Six Months After Fresh Human Islet Transplantation in a Type 1 Diabetic Patient.

*C. Socci, L. Falqui, A.M. Davalii, C. Ricordi, A. Secchi, C. Staudacher, P. Malti, G. Ferrari, P. Baro, S. Braghi, B. Fattor, F. Bertuzzi, F. Gavazzi, M. Freschi, P. Magistretti, V.Dicarlo and G. Pozza,*
*Milan, Italy.*

A 54 year old type 1 diabetic patient, bearing a kidney transplant, received intraportally 386,000 fresh human islets (equivalent number 586,000, Vol=1.07 ml) separated from one pancreas by the automated method. The islets were purified by centrifugation on a Ficoll gradients. A 7 day course of antilymphocyte globulin was added to the maintenance triple immunosuppressive therapy (CSA, AZA,

PRED). Strict blood glucose control (range 80-150 mg/dl) was maintained for three weeks by continuous i.v. insulin infusion to keep the islets in a near resting state.

Stimulated C-Peptide raised from <0.15 to 6.4 ng/ml. Insulin requirement dropped from 55 to 14 U/day at three months when steroid and insulin therapy were suspended for two days. Fasting glycemia was 90 mg/dl, post-prandial level was 160 mg/dl and returned to 100 mg/dl 4 hours later. Free-insulin (10 to 35 uU/ml) and serum C-Peptide (2.0-5.8 ng/ml) ranged in the normal level. After the test prednisone (5mg/day) and insulin (10U/day) were reintroduced. The insulin requirement subsequently went down and 20 days later insulin therapy was stopped. Six month after the islet transplant the patient is normoglycemic and off insulin.

This result shows that human islet transplantation is a new procedure to replace endocrine secretion in diabetic patients.

## Double Blind Trial with Azathioprine and Steroids in Newly-Diagnosed IDD

*J. Silverstein, N. Maclaren, W. Riley, D. Radjenovic, R. Spillar Gainesville, FL.*

Immunosuppressive drugs have effectively maintained endogenous insulin release in newly-diagnosed IDD. An unblinded trial using azathioprine (A) has shown increased C-peptide (C-P) secretion compared to controls. This is an interim analysis of a double- blinded placebo-controlled randomized trial comparing 4 treatment regimens in patients with IDD of ≤ 2 wks duration: steroids + azathioprine (S+A), steroids + placebo (S+P), azathioprine alone (A), placebo alone (P). Patients had similar characteristics at onset except for a slightly lower C-P and C-P/GLU ratio in the S+A group (p=0.1 ):

| Onset | S+A (n=15) | S+P (n=17) | A (n=12) | P (n=15) |
|---|---|---|---|---|
| Age (yrs) | 13.7 | 13.6 | 13.3 | 14.5 |
| Hgb/AIC | 9.7 | 9.6 | 9.9 | 9.0 |
| Peak C.P. | 0.44 | 0.56 | 0.65 | 0.60 |
| C.P/GLU | 1.2 | 1.9 | 2.12 | 2.0 |

Metabolic status was evaluated at 3 monthly intervals by insulin dose (u/kg/d), HgbA1C, blood glucose, and C-P response to oral Sustacal. At the end of 1 yr, patients treated with A had significantly better metabolic status than did the 3 other groups:

| 1 Yr | S+A (n=12) | S+P (n=15) | A (n=9) | P (n=10) |
|---|---|---|---|---|
| HgbAIC | 7.7 | 7.2 | 7.1 | 7.5 |
| U/kg/d | 0.74 | 0.63 | 0.47 | 0.64 |
| Peak C-P | 0.48 | 0.42 | 0.75p<0.03 | 0.43 |
| C.P./GLU | 1.65 | 1 .58 | 2.98p<0.05 | 1.43 |

The S+A group maintained C-P production whereas C-P values decreased in the 2 placebo groups. Steroids alone were not better than placebo. These data indicate that azathioprine is effective but degree of response is dependent on residual β cell function at IDD onset. This supports the possible use of azathioprine in trials to prevent onset of IDD.

## The Clinical Relevance of Plasma Human C-pepside (CP) measurements in the management of patients with Diabetes Mellitus.

*S.A. McDermott, J.A. Galloway,* R.L. Brunelle, C.T Spradlin and J.H. Anderson**
*Indianpolis, IN (Introduced by John A. Galloway, * Indianapolis IN)*

Measurement of plasma C-peptide (CP) as a surrogate for endogenous insulin secretion is a routine procedure; however, its relation to other variables has not been systemically evaluated. Therefore, utilizing data from 11 clinical trials of insulin, proinsulin or sulfonylureas involving 2041 patients, we undertook a meta-analysis to investigate relationships between CP and a number of clinical variables, including body weight, insulin dose and serum insulin antibodies.

The correlation between baseline fasting and post-stimulus CP (Sustacal 8 ounces containing about 34 grams CHO) was > 0.95 for patients with a BMI < 29 kg/M$^2$ but decreased progressively as the BMI increased. The latter correlation was better preserved in established than in the insulin naive patients. A correlation between CP and insulin dose was observed only in normal-weight IDDM's. A comparison of the plots of the highest and the lowest quartiles of CP vs fasting blood glucose disclosed minimal effect of endogenous insulin secretion, as indicated by CP, on glycemic control.

Negative correlations were demonstrated between CP and antibodies to human insulin and duration of diabetes in IDDM but not NIDDM.

Conclusion: The routine measurement of CP in the clinical management of diabetes is of limited value, particularly in NIDDM with obesity.

## Aminoguanidine Treatment Inhibits Advanced Glycosylation Product Accumulation in Diabetic Retinal Vessels

*H.P. Hammes, K. Federlin, and M. Brownlee* Giesen, FRG New York, USA*

Treatment of 17-month diabetic rats with aminoguanidine HCI prevents the 18-fold increase in retinal acellular capillaries and other morphologic changes as effectively as islet transplantation (Diabetes 39 (1): 62A, 1990). To assess the role of advanced glycosylation product (AGP) inhibition in this effect, AGPs were quantitated in retinal vessels from 32-week old rats using integrated microscopic fluorimetry. Eyes were obtained from three groups of male Lewis rats: non-diabetics (NC), STZ- diabetic (DC), and STZ diabetics treated with aminoguanidine 25 mg/kg/day i.p. (AG-D). Retinal digests showed marked accumulation of PAS-positive material at branching sites of precapillary arterioles in DC vs. NC, but not in AG-D vs NC. AGP-specific fluorescence measured in identical fields of unstained preparations was 440±20 AU in DC, vs. 170±15 AU in NC (p <.01). In contrast, specific fluorescence in AG-D was 220±13 AU.

These data demonstrate that microvascular AGP accumulation proceeds the full development of experimental diabetic retinopathy, and suggest that aminoguanidine prevents retinopathy development by inhibiting AGP formation.

## MISCELLANEOUS

## COMPLICATIONS-CARDIOVASCULAR SYSTEM

### A New Classification of Non-obese NIDDM in Association with Arteriosclerotic Risk Factors.

*Kouichi Hirao, Kanagawa, Japan*

To clarify significance of non obese IDDM, 148 cases with NIDDM were selected and arteriosclerotic risk factors were compared after dividing them into following four groups.

1. Those who have been obese up to the present (group 1 )
2. Those who were obese in the past but not presently (group 11)
3. Non-obesity group (group III)
4. Those who have gained by i 0Kg or more than the body weight in their 20's but are not obese (Non-obese obesity group) (group IV).

   Incidence of hypertension (WHO, 1987), total Cholesterol (TC), HDL-cholesterol (HDL-C), TC/HDL-C ratio and triglyceride (TG) of the four groups were compared.

Results

1. Incidence of hypertension was higher in Groups 1, II and IV than in Group III (P <0.001).
2. TC level was higher in Group I than in Group III (P <0.05). There was no difference between the other groups.
3. TC/HDL-C ratio was lower in Group 111 than in groups 1, 11 and IV (P <0.01).
4. TG level was higher in Group I than lin Group II (P <0.01), and higher in Groups I, II and !V than in Group III (P <0.001).

(Conclusion)

1. Group III is obviously different from all other groups in respect of complications with hypertension or lipometabolic disorder. 2) Those who gained weight by 10 Kg or more compared to their early 20's show the same pathological manifestations as the obesity group even if they are presently not obese. 3) The above findings suggest that diabetic patients who are presently classified as non-obesity type but were obese in the past should be treated differently from non-obesity type diabetics in view of the complications with arteriosclerotic risk factors such as hypertension and lipometabolic disorder.

### Coronary Heart Disease and Diabetic Retinopathy in Newly Diagnosed Diabetes in Da Qing, China

*HU Ying-Hue, Pan Xiao-Ren, Barbara V. Howard, Peter H, Bennett Da Oing and Beijing China.*

In 1986, 108, 682 of 280,000 residents of the city of Da Qing were surveyed. Based on results of 75g oral glucose tolerance tests 630 (0.58%) subjects (296 males, 334 females) ware found, with previously undiagnosed diabetes according to 1985 WHO criteria. These subjects, and 521 of similar age and sex with normal glucose tolerance were examined to determine the prevalence of retinopathy and coronary heart disease and identify associated characteristics.

Retinal examinations of 440 newly diagnosed diabetics showed that 15.2% had microaneurysms, 6.8% had hard exudates, 5.5% soft exudates and 2.3% proliferative retinopathy. Among the controls 2% had only one or two microaneurysms. Coronary heart disease, according to criteria used by the WHO Multinational Study based on Minnesota coding of resting electrocardiograms, was ten times more frequent in the diabetics (4.4%) than in the controls (0.4%).

Logistic regression analysis showed that plasma glucose level (after adjustment for age, BMI and blood pressure) and HDL-C (after adjustment for age, blood pressure, plasma glucose, BMI and plasma triglyceride) were associated with CHD among the diabetics. Plasma glucose level was a risk factor for retinopathy after adjusting for age, hypertension and plasma triglyceride.

Both micro and macrovascular complications occur frequently in previously undiagnosed Chinese diabetics and the frequency of coronary heart disease is markedly increased compared to the low frequency among Chinese nondiabetics.

### Insulin Resistance is Associated with Coronary Heart Disease in the Elderly

*L. Mykkanen, M. Laakso, and K. Pyorala*
*Kuopio Finland.*

Hyperinsulinemia has been shown to be a risk factor for coronary heart disease (CHD) in middle-aged subjects. Hyperinsulinemia is an indicator for insulin resistance which is in addition characterized by high systolic blood pressure, high serum total triglyceride and low HDL cholesterol levels. We created an insulin resistance score, a sum of these four risk factors, and investigated its association with the prevalence of CHD in a nondiabetic population sample of 396 men and 673 women aged from 65 to 74 yr. There was no association between fasting plasma insulin and the prevalence of definite or possible myocardial infarction (11.2, 15.8 and 15.6 &; insulin quintiles I + II, Ill + IV, V) or ischemic ECG changes (44.1, 50.6 and 50.6%) in men whereas in women the prevalence of myocardial infarction (5.2, 3.7 and 10.4%; p = 0.09) and ischemic ECG changes (36.3, 42.4, 45.5%; p = 0.06) tended to increase by insulin quintiles. In women, the prevalence of definite or possible myocardial infarction increased by quintiles of insulin resistance score (3.7, 4.9 and 12.6%; p <0.01 ) whereas in men this increase was less marked ( 11.2, 14.9 and 17.9 % ; p = NS). In both sexes, the prevalence of ischemic ECG changes (40.4, 50.6 and 59.7% in men, P <0.01; 35.5, 41.1 and 53.2% in women, p <0.01) increased by quintiles of insulin resistance score. Thus, in the elderly insulin resistance score is stronger associated with an increased prevalence of CHD than fasting insulin level.

### Serum Lipid and Lipoprotein levels in relation to Diabetic Control in a population of Malaysian NIDDM patients

*W B. Wan Mohamad, N. Mafauzy, M. Mazidah and B.E. Mustaffa*
*Hospital Universiti Sains Malaysia, 15990 Kelantan.*

237 (128 males and 109 females) IDDM patients were studied to define the alteration in serum lipid and lipoprotein levels and its relation to diabetes control. An overnight fasting blood were analysed for (fasting) serum triglyceride (TG), total cholesterol (T-Cho1), LDL Cholesterol (LDL-Chol) and glycosylated haemoglobin (HbA1).

118 patients were considered to have good control with an HbA1 of less than 8.5% (group A), 63 fair control (HbA1 between 8.5 to 10%) (group B) and 56 had poor control with HbA1 greater than 10% (group C). There were no statistically significant difference in the BMI, age and sex of patients in the three groups.

Mean (±S.D) fasting TG, T-Chol, LDL-Chol and HDL- Chol were 2.43± 1.94, 5.82± 1.31, 3.91± 1.25 and 0.92± 0.52 mmol/l respectively. Mean values (± S.D.) for TG in group A, B and C were 2.06 ± 1 .56, 2.56 ± 1 .65 and 2.80 ± 1 .62 mmol/l and the corresponding values for T. Chol were 5.64 ± 1.12, 5.96 ± 1.23 and 6.08 ± 1.39 mmol/l. LDL-Chol levels were(mean± S.D.)3.85± 1.23, 3.95± 1.26 and 4.18 ± 1.33 mmol/l in group A, B and C respecitvely while the HDL-Chol values were (mean ± S.D.) 0.92 ± 0.37 mmol/l in group A, 0.96 ± 0.66 mmol/l in group B and 0.73 ± 0.35 mmol/l in group C.

Conclusion: 1) TG and T-Chol values in group C patients were significantly higher compared to those of group A ($p < 0.003$ and $p < 0.002$). 2) HDL-Chol was significantly lower in group C patients in contrast to that of patients in group A or B ($p < 0.001$ and $p < 0.003$) respectively.

These data further support the observation that poorly controlled NIDDM is associated with raised serum triglyceride and total cholesterol levels and a reduction in the cardioprotective HDL-Cholesterol. The importance of tight glycaemic control to normalise serum lipids and lipoproteins in patients with diabetes mellitus is emphasised.

## Incidence of Hypertension by Glucose Tolerance in Pima Indians

*OZ Liu, Mf Saad, Rg Nelson, Ma Charles, Djpettiti, Wc Knowler, Phoenix, AZ, USA.*

The incidence of hypertension (WHO criteria) was determined in 2544 Pima Indians aged > 15 years, initially free of proteinuria by Labstix. During a mean of 7.7 yrs follow-up, hypertension developed in 243 of 1905 subjects with normal glucose tolerance (NGT), 69 of 254 with impaired glucose tolerance (IGT), and 165 of 385 with NIDDM. The 5-year cumulative incidence rates of hypertension in NGT, IGT, and NIDDM were 5%, 15%, and 15%; and the 10-year rates were 13%, 29%, and 39%, respectively. Adjusted for age, sex, and body mass index (BMI), the incidence of hypertension in NIDDM was 1.7 times (95% confidence interval, CI = 1.3-2.1) that in NGT; and in IGT was 1.6 times (95 % CI = 1.2-2.2) that in NGT.

In non-diabetic subjects, male sex, older age, higher mean blood pressure (MBP), lower serum cholesterol concentration, and BMI predicted hypertension. In diabetic subjects, older age, higher MBP, lower serum cholesterol concentration, and insulin treatment, variables measured at the first diabetic examination, predicted hypertension.

In Conclusion 1) the incidence of hypertension is increased in IGT and NIDDM, despite the subjects being free of proteinuria at baseline, 2) BMI is a risk factor for hypertension only in nondiabetic subjects, and 3) insulin treatment predicts hypertension in diabetes.

## Impact of Insulin Resistance on Blood Pressure in Patients with Type 2 Diabetes (NIDDM)

*K.I. Birkeland, F Chatzipanagiotou, KF. Hanssen and S Vaaler,*
*Oslo, Norway.*

An association has been reported between insulin resistance and blood pressure in non-diabetic normal weight hypertensives. We raised the question whether degree of insulin resistance is related to blood pressure in type 2 diabetes.

Twelve women and 15 men with type 2 diabetes for 3-14 (8) years, treated with diet alone (2) or combined with peroral hypoglycemic agents (25) were examined 3-monthly for 10-24 (17) months. The subjects' mean HbAlc during the study period was 6.8-11 .7 (8.6)%, BMI 20.8-31.5 (26.4) kg/$m^2$, fasting insulin 0-52 (13) mU/I, C-peptide 0.3-1.47 (0.77) nmol/l, diastolic blood pressure (DBP) 79-111 (95) mmHg, systolic blood pressure (SBP) 124-209 (151)mmHg and mean blood pressure (MBP) 96-138 (114)mmHg. Waist/hip (W/H)-ratio was 0.78-1.01 (0.93), and glucose disposal rate (GDR) during a 2 hours euglycemic insulin clamp 2.01 - 9.13 (4.29) mg/kg/min.

A stepwise regression analysis chose GDR and W/H-ratio as significant independent variables to account for variations in blood pressure. There were significant negative correlations (Spearman) between GDR and DBP ($r = 0.50$). SBP ($r = 0.45$) and MBP ($r = 0.48$). We conclude that blood pressure is significantly related to insulin resistance in type 2 diabetic patients.

## Effect of propionyl-L-carnitine on cardiac function in streptozotocin-induced diabetic rats

*N. Hotta, T. Terada, H. Matsubara, N. Koh, F. Sakakibara and N. Sakamoto*
*Nagoya, Japan.*

Numerous experimental studies have indicated a link between diabetes-induced abnormal lipid buildup in the myocardium and the development of cardiomyopathy. It is also known that L-carnitine has an important role on (3-oxidation of lipid metabolism and its levels in tissues are low in diabetic state. We investigated whether or not the oral administration of propioyl-L-carnitine(PC), an analogue of L-carnitine can improve the cardiac dysfunction in diabetic rats using working heart preparation.

PC(3g. $Kg^{-1}$. $day^{-1}$. P.O) were given for 4-wk period 2 days after diabetes induction. Either PC or insulin (Ins;4U.$day^{-1}$. s.c.i.) treatment alone partially improved cardiac dysfunction in diabetic rats. However, the combination treatment with them significantly improved in heart function (Ex., LVDP (mmHg) under 15 cmH20 artrial filling pressure (n=6-10); Normal, DM, DM+PC, DM+Ins, DM+PC+Ins=110 ± 10, 79 ±4, 93± 10, 85±9, 112± 6 respectively; $p<0.05$ DM VS DM+PC+Ins). This preventive effects of PC, Ins or their combination treatments coincide with a significant decrease in the myocardial triacylglycerol levels and increase in its carnitine contents.

The data suggest that a possible correlation may exist between elevated triacylglycerol levels and decreased carnitine contents in the myocardium, and cardiac dysfunction in diabetic rats, suggesting PC treatment to be useful therapy for diabetic cardiomyopathy.

### Duplex Sonography of the Carotid and Femoral Arteries in newly diagnosed Type 2 Diabetics.

*Jana Brunova, Josef Bruna, Jiri Valek,*
*Prague, CSFR*

The duplex sonography of carotid and femoral arteries were made in group 107 newly diagnosed Type 2 diabetic men, aged 45-64 years. The atherosclerotic changes of arteria carotis were found in 44% of group and changes of peripheral arteries in 61.7% . However arterial stenoses were mostly non-significant.

Diabetics with atherosclerotic changes of investigated arteries had significantly increased ischemic heart disease compared with diabetics without peripheral atherosclerosis ($p < 0.01$). Diabetics with the macrovascular disease had significantly higher levels of triglycerides, total cholesterol/HDL-cholesterol ratio and insulinemia than diabetics without ultrasonographically diagnosed atherosclerotic lessions.

Results of our study confirmed that duplex ultrasonography is the usefull method in diagnosis of early atherosclerotic arterial changes.

## COMPLICATIONS-NEPHROPATHY

### A New Sensitive ELISA Test for Spot Analysis of Urinary Albumin

*Dana Driskell, Kenneth Marbut, James Lane, Margaret MacDougall, Mark Colwell, Thomas Wiegmann*
*Kansas City, Ks. and Kansas City, Mo.*

Albumin specific qualitative testing of morning urine has been advocated for screening diabetic patients. We have shown (Diab Care 13:864, 1990) that the commonly used level of 30 µg/ml is very specific but insensitive. Therefore we examined the utility of a new ELISA test kit (20 µg; Procene, Inc.) We compared kit results with specific albumin concentration (RIA) in spot and timed 24 hr collections. Random patients with type II diabetes and hypertension (N =68) were recruited. Spot urine samples were obtained at time of outpatient visit at various times of day and timed collections from the preceding 24 hrs. Albumin excretion rate AER > 20 µg/min (separator value) was present in 46% of patients. Spot and 24-hr albumin concentrations were highly correlated with each other and with AER ($R > 0.850$, $p < 0.001$). Receiver operating characteristics were determined. At the separator 20 µg/min, the kit had a specificity of 42% and a sensitivity of 90% in random urine samples (74% and 97% in 24-hr urine). Random urine specimens with a low threshold screening test (20 µg/ml) provide for a highly sensitive screening test in a high risk population. Specificity improves with extended urine collection.

### Effects of moderate changes in Dietary Protein intake on Microalbuminuria in type I Diabetic Patients

*C. Percheron, C. Colette, N. Pares-Herbute, L. Monnier, Montpellier (France).*

Changes in urinary albumin excretion (UAE) were observed when diabetic patients were submitted to drastically restricted or enriched protein diets. However, the compliance to such diets remain questionable. For that reason, we studied the changes in microalbuminuria with diets closer to usual nutritional recommendations. Ten diabetic were randomely allocated to 3 diets with different protein contents (g/kg ideal body weight/day): 0.84±0.01 (period 1); 1.36±0.09 (period II); 2.07±0.10 (period III). Urinary samples were collected on the 3 last days of each 3 week-period. UAE means (mg/day)±SEM were: 33.6±16.7 (I); 50.4 ± 20.4 (II); 52.6± 19.3 (III); $p < 0.01$ between III and I and between II and I. Creatinine clearance means (ml/min/1.73 m2) ±SEM were 97.0± 8.2 (I); 99.9± 9.2 (II) 123.4 ± 5.4 (III); $p < 0.01$ between III and I and $p < 0.05$ between III and II. Urinary urea excretion means (mmol/day) ± SEM were: 334 ± 34 (I); 441 ± 54 (II); 602 ± 4g (III); $p < 0.01$ between all periods. HbAl, body weights and blood pressures remained stable over all periods. Significant positive linear relationships were found first between absolute changes in UAE from period II to I or III and the corresponding relative changes in protein intakes ($p < 0.01$ ), and second between creatinine clearances and protein intakes ($p < 0.05$). These results indicate that the diminution in UAE with progressive protein restriction is a continuous phenomenon and that no "threshold zone" can be individualized when protein intakes are maintained within reasonable limits.

### Screening for Microalbuminuria in Diabetics: Comparison of Combur-test dipstick (CTD), Microbumintest reagent tablet (MBT), Immonoturbidimetric assay (ITA) and Double Antibody Radio immunoassay (RIA)

*M. Musalmah, W.B. Wan Mohamad, M. Mafauzy and B. E. Mustaffa Kota Bharu, Malaysia.*

Small increases in albumin in urines of diabetic patients are early signs of nephropathy. Detecting microalbuminuria is important because early intervention of diabetic nephropathy may prevent or delay further deterioration of renal function. However accurate quantification requires sensitive assays such as RIA. For screening purposes, a rapid, simple and cheaper method is desirable. We thus compared the performance of the above methods in measuring albumin in randomly collected spot urines of 247 diabetic patients.

The correlation coefficients of CTD, MBT and ITA vs RIA were 0.73, 0.50 and 0.94 respectively. Their ability to detect urinary albumin ≥ 30 mg/L compared directly with RIA were respectively as follows: accuracy 91%, 88%, 90%; sensitivity 83%, 99%, 100%; specificity 99%, 81%, 86% false positives 0.8%, 23%, 16% and false negatives 16%, 1%, 0%. Thus the performance of MBT in detecting microalbuminuria was comparable to that of ITA and may be use to screen urine samples for later determination with RIA.

### Evaluation of a Sensitive Urinary Albumin Assay on a Boehringer Mannheim/Hitachi 704 Analysis System

*A. Hubbuch, F.S. Lang, M. Kaupat*
*Boehringer Mannheim GmbH, D-6800 Mannheim*

We have evaluated a new immunoturbidimetric assay for the determination of urinary albumin by automated analysis using the Boehringer Mannheim/Hitachi analysis systems 704. Turbidity is measured bichromatically by the equilibrium method at 340/700 nm. Calibration is made by 5 standards ranging from 0 to 350 mg/L albumin. Results: Within run CVs (n=21) were below 3% from 10 to 160 mg/L, day to day CVs (d=10) below 4% when using a fixed calibration curve. Calibration is stable for 2 weeks, if the reagents are stored in the instrument.

The measuring range extends from 3 to 400 mg/L. Good agreements were found between the results of Hitachi 704 and 717 (y = 0.7 +1 .00 x, r =0.999, 37°C), and between the new reagent on Hitachi 717 and a nephelometric assay (x): y = 1.5 + 1.04 x, r = 0.992. No reagent dependent carry over was found with 44 other Boehringer Mannheim system reagents. No interference was observed with 18 drugs tested "in vitro" and with endogenous urine components tested at pathological concentrations.

It should be noted that not only albumin, but also creatinine and BNAG and be measured in the same (undiluted) urine on this and other Boehringer Mannheim/Hitachi anlayzers.

In conclusion, the new reagent allows a convenient and reliable determination of urinary albumin at the low concentration level needed for early diagnosis of glomerular damage in diabetic nephropathia.

## Risk Factors for Renal Mortality in Diabetes

*JH Fuller, L.K Stevens and the WHO Multinational Study Group*
*London, England.*

Factors related to subsequent renal mortality have been studied in a 7 year follow-up of 4740 middle-aged diabetic subjects from 10 international centres participating in the WHO Multinational Study. Out of a total of 542 deaths. 76 (14%) had renal disease (International Classification of Diseases 250.3, 580-589) assigned as the underlying cause of death by a mortality committee. In three centres, Arizona, Hong Kong and Tokyo, death rates from renal disease exceeded those from ischaemic heart disease.

The presence of proteinuria at the base-line examination was the strongest predictor of renal mortality in both insulin-dependent diabetes (IDDM) and non-insulin-dependent diabetes (NIDDM) with age-and sex-adjusted relative risks (RR) of 12.1 and 10.7 respectively. The relationship of systolic blood pressure (SBP) to renal mortality was nonlinear, with marked increases in risk for SBP $\geq$ 146 mmHg vs SBP $\leq$ 128 mmHg: RR: 8.0(IDDM); 6.3 (NIDDM). Age-adjusted renal mortality rates increased significantly with diabetes duration in both IDDM and NIDDM.

These findings have implications for the planning of risk factor interventions for the prevention of renal mortality in diabetes.

## Natural History and Risk Factors for Nephropathy in Non-Insulin Dependent Diabetes Mellitus.

*M.D. Yassine, D.E. Prior*, V.M. Hawthorne, W.H. Herman**
*Ann Arbor, MI.*

Non-insulin dependent diabetes mellitus (NIDDM) is a leading cause of renal failure in the United States. We performed a retrospective cohort study and nested case-control study to define the natural history and risk factors for nephropathy in NIDDM.

We reviewed the medical records of 704 patients with NIDDM who were admitted to the University of Michigan Hospital between 1978 and 1987. Diabetic nephropathy was defined by persistent proteinuria > 0.50 grams per 24 hours. All 80 subjects with diabetic nephropathy and a sample of 72 subjects with urinary protein excretion < 0.15 grams per 24 hours were enrolled in the case control study.

The cumulative incidence of diabetic nephropathy increased with duration of diabetes (1% at 5 yr, 5% at 10 yr, 11% at 15 yr, 33% at 20 yr, and 45 % at 25 yr). Older age at diagnosis of diabetes (Odds Ratio (OR) = 2.35, 95% Confidence Interval for OR (95% CI) = 1.35, 4.08) and obesity (OR = 1.58, 95% CI = 1.04, 2.42) were significantly associated with risk of nephropathy. In the case-control study, longer duration of diabetes (OR = 22.78, 95% CI = 6.35, 81.77), higher glycosylated hemoglobin (OR = 3.28, 95 % CI = 2.61, 8.56), higher triglyceride levels (OR = 5.12, 95 % CI = 1.93, 13.52) and higher systolic blood pressure (OR = 3.64, 95% CI = 1.35, 8.87) preceding the diagnosis of proteinuria were associated with increased risk.

We conclude that the risk of nephropathy in NIDDM is similar to that observed in IDDM, but that risk factors may differ. The lower prevalence of nephropathy observed in cross-sectional studies of NIDDM may be related to the increased cardiovascular mortality of patients with NIDDM and nephropathy.

## Effects of hypoproteic diet and captopril on the proteinuria hyperexcretion in type 1 (insulin-dependent) diabetic patients

*J.A. Arroyo, R. Sola, J.M. Mallafre, J. Soldevila, M. Balsells, X. Ampudia and J.M Pou.*
*Barcelona. Spain.*

Several studies have shown that a certain number of type 1 (IDDM) patients have microalbuminuria, highly predictive of later developement of proteinuria. The factors responsible for progress from microalbuminuria to macroproteinuria are still unclear.

We studied the macroproteinuria in a selected group of IDDM (14 patients, 7M and 7F.) with good metabolic control (HbA1c 7.2±1.5%). They were treated with moderate restriction proteins (A) or captopril 100 mg/24 hs(B), for 3 months in a crossover study (design 3 months of wash-out in between). Blood pressure (BP) was similar (Saluretic was added in both periods in all diabetics and nifedipine (Nif) in 5 p. in A and 4 p. in B group). Macroproteinuria was expressed as mg/24.

RESULTS: PROTEINURIA

| | Pre-therapy | Post-therapy | P |
|---|---|---|---|
| A. | 1254±200 | 789±7g | p<0.005 |
| A+Nif | 1145±139 | 987±106 | p<0.05 |
| B. | 1398±159 | 805±59 | p<0.005 |
| B+Ni. | 1198±98 | 985± 107 | NS |

Creatinine levels and Plasma lipids did not change both hypoproteic diet or captopril

Conclusions: Restriction on protein intake and captopril administration promoted a decrease in proteinuria in nephropatic diabetic patients without glomerular change or hyperlipidemia. Nifedipine prevent the beneficial effect of captopril, and partially the effect protein restriction.

## Therapeutic Effect of an Orally Administered Prostaglandin EI (PGEI) Derivative in Patients with Diabetic Nephropathy

*S. Watanabe[1]. T. Ogihara[1], S. lyori[1], H. Kaneshige[2], Y Nomoto[2], H. Sakal[2]*

Department of Internal Medicine. Hiratsuka City Hospital, and Department of Internal Medicine, Tokai University, Japan.

Intravenously administered PGEI, as ii promotes vasodilation and reduces platelet aggregation, has been reported to be useful for treating diabetic nephropathy. Accordingly, the aim of this study was to evaluate the therapeutic effect of an orally administered PGEI derivative in patients with diabetic nephropathy. Eighteen patients diagnosed with diabetic nephropathy were administered this drug at a daily dose of 30μg for six months. These patients showed neither serum creatinine (s-Cr) levels higher than 1.3 mg/dl nor urinary albumin excretion levels higher than 300 pg/min. Urinary albumin excretion within a 24 hour period and various clinical parameters were evaluated monthly before and after 6 months of treatment.

A significant decrease in the urinary albumin excretion was observed without relation with the levels of the urinary albumin excretion before the start of treatment. Further, the urinary NAG excretion tended to decrease after treatment. Also, the levels of urinary throboxane B2 significantly decreased with the reduction of the urinary albumin excretion.

From the above results the authors have concluded that the administration of this oral PGE1 derivative is useful for treating patients with a mild diabetic nephropathy.

Diabetic Nephropathy: ~1lhen to Treat

T Tetsutani, T. Yamaguchi, K. Kadona, and K Yasunaga The first Dapariment of Internal Medicine. Kansai Medical University, Moriguchi Osaka, Japan

In 86 patients with non-insulin dependent diabetes mellitus who wei negative for proteinuria by a test paper method, the albumin excretic rate (AER) was compared to the albumin/creatinine ratio, and baseline albumin/creatinine ratio value was determined at whic therapy to arrest the progression ot nephropathy should be initiate~ The urine samples obtained during ambulation. The reproducibility ~ time-restricted urine sampling was investigated by the rate ~ creatinine excretion. The mean coefficient of variation was found ' be 42 %, and inaccurate urine sampling appeared to cause variatic in the AER. A significant difference was evident between males an females in creatinine excretion (0.823±0.152 mg/min for males an 0.577±0.182 mg/min for females, $p < 0.001$ ).

The baseline albumin/creatinine ratio value for initiating therapy w~ established to be 36 mg/g crea. for males and 51 mg/g crea. fc females.

Use of the albumin/creatinine ratio appears to provide a simple an valuable index for determining when to initiate therapy for diabeti nephropathy.

Short-term and long-term Effects of Urokinase on Patients with Diabetic Nephropathy

H. Sakai", S. Watanabe, M. Yagame, H. Kaneshige, and Y Nomot~ Isehara. Japan.

Renal biopsy specimens from many patients with diabeti

INTNL. J. DIAB. DEV. COUNTRIES (199i), VOL. 11

nephropathy show deposition of fibrin/fibrinogen in the glomeruli. The aim of this study was to evaluate effects of urokinase on patients with diabetes nephropathy.

Twenty nine NIDDM patients with diabetic nephropathy were randomly divided into two groups: 1 ) Twelve patients treated with weekly intravenous administration of 60,000 units of urokinase and daily oral administration of 150 mg of diyridamole, and 2) 17 patients with dipyridamole alone. None of the patients showed more than 3.5 mg/dl of serum creatinine at the beginning of this study. Short-term effects were evaluated by the degree of urinary protein, and the longterm effects by the degree of decrease in the slope of reciprocals of serum creatinine levels. Statistical significance was evaluated by the MannWhitney U test and chi square test.

There was a significant decrease in the amount of urinary protein in patients treated with urokinase and dipyridamole compared with those given dipyridamole alone. With respect to the longterm effects, a significant maintenance of renal funetion was observed in patients given dipyridamole and urokinase. There were no severe side effects throughout the study period.

It was concluded that combined therapy of urokinase and dipyridamole is effective in the improvement of proteinuria, and in the maintenance of renal function in patients with diabetic nephropathy.

Reversal of Advanced Glycosylation Endproduct (AGE) Levels by Kidney Transplantation but not by Hemodialysis

Z Makita, E.J. Raytield, Z. Yang, Y Horii, E.A. Friedman, A. Cerami, and H. Vlassara

New York, NY.

It is well known that diabetic nephropathy patients on hemodialysis develop vascular complications at an accelerated rate with far g reater mortality than patients having received renal transplants. We have shown that serum AGE levels in diabetic hemodialysis patients are markedly elevated. To examine the effect of dialysis vs kidney transplant on circulating AGE levels, we tested pre and post-dialysis, as well as pre-and post- kidney transplantation sera, using an AGEspecific radio-receptor assay. Sera from 8 normal (NL) subjects, 8 diabetics on hemodialysis (DHD), 8 non-diabetics on hemodialysis (NDHD) as well as 12 diabetics with kidney transplants were tested before and after dialysis or transplantation. Post-dialysis sera contained modestly lower AGE levels than pre-dialysis sera (NDHD 20.3±5.1 vs 25.4±7.5 AGE U/ml, $p < 0.01$, DHD 57.1±11.0 vs 75.2±1 7.5 AGE U/ml, $p < 0.025$), but neither group returned to normal levels (15.6±3.4). In contrast, AGE levels in transplanted patients (DKT) were markedly decreased (25.6±7.4 AGE U/ml) as compared to non-transplanted post-dialysis DHD ($p < 0.001$). Of note, one transplant patient exhibited sharply reduced AGE levels as compared to pre-transplant levels just 4 days after transplantation (20.6 vs

80.1 AGE U/ml). These data indicate that hemodialysis is an ineffective treatment modality resulting in AGE serum accumulation with subsequently vascular morbidity and mortality. Thus, optimal renal clearance such as thatestablished by kidney transplantation is necessary for etficient AGE removal.

The Possibility of A New Treatment for Diabetic Neuropathy by Trial of Thromboxane Synthetase Inhibitor

Yuri Ono, Masahiko Kotoh, Mamoru Kudoh and Shoichi Nakagawa Sapporo, Japan.

Considering vascular factors in the progression of diabetic neuropathy, we investigated the effect of thromboxane synthetase inhibitor on the peripheral nerve function and skin blood flow of
diabetics with neuropathy as to whether it could affect diabetic neuropathy.

Eleven diabetic patients with neuropathy were given thromboxane synthetase inhibitor CV-4151 for 8 weeks and were examined for alteration of nerve conduc:tion velocity (NCV), vibratory perception threshold (VPT), skin blood flow by laser Doppler flow meter and deep skin temperature in 4 extremities, and the changes of plasma thromboxane Bz (TXBz) and plasma prostaglandin F~a (PG). After ad-ministration of CV-4151, plasma TXBz level decreased, and plasma PG-level increased significantly. As a result, the plasma TXB2/PG ratio dropped signifioantly to lower than that ef before. NCV and VPT in 4 extremities showed significant improvement. Deep skin temperature and skin blood flow also improved significantly. It appears that thromboxane synthetase inhibitor given to diabetics decreases TXA2 production and increases PGIz production, improving the TXAz/PGIz ratio; as a result, it is presumed that blood flow in nerve systems increases, improving their functions. In conclusion, vascular abnormalities are proposed to be one of the most important pathogenesis of diabetic neuropathy, so that the thromboxane synthetase inhibitor which improves the TXBz/PGIz ratio and blood flow can be used for the treatment of diabetic neuropathy.

Immediate Reduction of GFR During Aldose Reductase Inhibition in Normoalbuminuric IDDM Patient

Margrethe Mau Pedersen", Jens Sandahl Christiansen, Carlerik Mogensen

Aarhus Denmark.

To follow up our previous finding that 6 months of aldose reductase inhibition reduces glomerular hyperfiltration in normoalbuminuric insulin dependent diabetic patients, 14 such patients were randomized to receive 14 days of ponalrestat (Statil) 600 mg daily (n=8, age 35±7 (SD) yrs, diabetes duration 12±6 yrs, BMI 23.1±1.7 kg/mz, HbA~~ 7.9±0.9 %) or placcebo (age 37±g yrs, diabetes du ration 15±7 yrs, BMI 25.0±2.0 kg/mz HbAi~ 8.2±1.0% ). Glomerular filtration rate (GFR) (clearance of ~z51-iothalamate) and renal plasma flow (RPF) (clearance of ~3~1- hippuran) were assessed on day 0, 3 and 1 4. During ponalrestat GFR showed a statistically significant reduction from 131±5 (SE) ml/min/1.73mz to 1 18±4 on day 3 ($2p<0.01$ ) and 115±4 on day 14 ($2p<0.01$ ). RPF was likewise reduced from day 0 to day 3: 530±23 vs 485±23 ml/min/1.73mz (~$p<0.01$) while a borderline significant reduction from day 0 to day 14 appeared (489±23). Filtration fraction (FF) was not significantly changed. During placebo no changes in GFR (142±7; 141±5; 140±7), RPF or FF were observed. Blood pressure was unaltered with both ponalrestat and placebo.

These findings confirm that aldose reductase inhibition also in human diabetes ameliorates early functional renal abnormalities. The prompt effect suggest that the underlying mechanism is of functional rather than morphological nature.

COMPLICATIONS-NEUROPATHY

A 6 month randomised controlled study of Ponalrestat in diabetic cardiac autonomic neuropathy.

M.J. Abrahamson, E. Beale. F Bonnici, J. Kalk, W Mollentze, H. Nel, L.I. Robertson

Depts ol Medicine, Universities ot Cape Town, Orange Free State, Witwatersrand and Addington Hospital, Durban, S. Alrica.

The effects of Ponalrestat 600 mg/day on cardiac autonomic function were examined in 95 diabetics (75 IDDM, 20 NIDDM) aged 18-65 yrs with severe asymptomatic cardiac autonomic neuropathy (CAN) (E:I



ratio < 5th percentile for age). Patients participated in a 6 month double-blind randomised placebo- controlled study. Tests of CAN (E:I ratio, heart rate response to Valsalva manoeuvre and to standing (30:15) were performed using the O-Med NDX monitor 1 device (Q-Med International, New Jersey, USA). Ponalrestat was well tolerated with no serious adverse events encountered. Glycaemic control (HbA~c Ponalrestat group 11.8±3.2%, placebo group 12.3±3.3% at entry (normal 6-9%) remained unchanged during the study. No significant change in CAN occurred in either group as shown:

PONALRESTAT I PLACEBO

n entry completion ~ n entry completion

E:I 45 1.079±0.06 1.073±0.05, 41 1.080±0.06 1.086±0.07
Valsalva 16 1.189±0.17 1.211±0.2 13 1.206±0.13 1.189±0.09
30:15 28 1.097±0.11 1.093±0.11 ~ 29 1.065±0.09 1.05±0.10

The absence of change in CAN in both groups may in part reflect suboptimal dosage duration of therapy, or the relatively advanced stage of CAN at entry into the study. Long term trials in patients with less severe CAN are warranted.

Omega-6 Essential Fatty Acid Treatment Promotes Capillary Growth and Prevents Neuromuscular Dysfunction in Diabetic Rats

M.A. Cotter, N.E. Cameron and S. Robertson Aberdeen, Scot/and.

In diabetes, a deficit in 6-desaturation limits linoleic to gammalinolenic acid conversion. This reduces prostacyclin production, an important vasodilator controlling local blood flow. The aim was to test whether gamma-linolenic acid treatment, using evening primrose oil (EPO) (Efamol, Scotia Pharmaceuticals), could prevent altered nerve and muscle function, and improve vascular supply. A nondiabetic and 2 streptozocin-diabetic (45 mg/kg i.p) groups of male rats were used. One diabetic group was given 10 % dietary supplementation with EPO for 2 months. In final experiments (1-1.5g/kg urethane anaesthesia) nerve conduction velocity (cv) resistance to hypoxia, & slow soleus & fast extensor degitorum longus (EDL) contractile properties were measured. Capillaries in these tissues were stained for alkaline phosphatase. For sciatic nerve, capillary density was unaffected by diabetes but was 20% increased with treatment. 27% and 8% increases in capillarization were also seen for EDL, and soleus muscles respectively. 12%

Sensory and 29°/ motor CV deficits and a 49% increase in hypoxic resistance were prevented by EPO. For soleus muscle a diabetes-induced slowing of maximum contraction and refaxation rates was ameliorated. For EDL a 21°l° reduction in tetanic tension was also prevented.

Metabolic Correction with Myoinositol Retards the Development of Chronic Diabetic Neuropathy in the BBlW rat

S. Lattimer, S. Chakrabarti, DA Greene, Aaf Sima. Ann Arbor, MI and Winnipeg, Canada.

Altered myoinositol (MI) metabolism has been implicated in the acute but not the chronic structural and functional peripheral nerve defects in the diabetic rat. Spontaneously diabetic BB/W rats were treated with 1% dietary MI or the ARI statil (20 mg/kg/d) for 6 mos and compared to non-diabetic controls or untreated BBIW rats. Nerve conduction velocity (NCV) was determined monthfy, and sciatic nerve MI content and sural nerve morphometry determined at end of study. HbAlc was similar in all diabetic groups.

Dietary MI or ARI completely prevented ihe diabetes associated reduction in sciatic nerve MI (control 2.96±0.22; untreated i .97±0.22;

MI 2.68±0.23; ARI 3.06±0.25 wmol/g, all $p < 0.05$ vs untreated), and partially prevented the slowing of NCV (control 49.9± 1.3, untreated 40.6 ± 1.3; MI 44.2 ± 0.6; ARI 44.8 ± 0.8 Mlsec, aIl $p < 0.01$ vs untreated). NCV correlated inversely with axo-gfial dysjunction ($p < O,OOOt$ ). Axonal atrophy (axonlmyelin ratio and myelin wrinkling) was completely prevented by MI and ARI (all'$p < 0.02$). Axo-glial dysjunction was partially prevented to a smiliar degree by both MI and ARI ($p < 0.001$ ). Nerve fiber regeneration was increased in diabetic rats by MI and ARI, but to a greater extent by the latter (control 1.3±0.4°/ ; untreated 5.2±1.7%; MI 11.1±1.4%, ARI 15.5±2,3°/, $p < 0.05$). Conclusion: All currently defined ARI-sensitive functionally relevant structural defects in diabetic rat nerve resembling those in diabetic neuropathic patients are corrected by MI supplementation, and are thereby attributable to alterations in MI metabolism induced by polyol pathway activation.

Treatment of diabetic neuropathy by gamma-linolenic acid as evening primrose oil (Efabetic) Efabetic Multicentre Trial Group

(Coordnator, GA Jamal, Glascow, United Kingdom).

Many studies have shown that in diabetes there is impaired conversion of linoleic acid to gamma linolenic acid (GLA) and further metabolites. Since those metabolites and their eicosanoid derivatives are important in nerve membrane structure and in the microcirculation, it is possible that reduced GLA formation may be important in the pathogenesis of diabetic neuropathy. Severaf animal studies and a pilot placebo-controlled human study in 22 patients showed that GLA administered as evening primrose oil (EFO, Efabetic) could both prevent and reverse diabetic neuropathy.

101 patients were therefore entered into a 7-centre, placebo-controlled study of EFO. Patients were randomised to receive 6g/day of EFO or placebo for one year on a double-blind basis. At baseline and at 3,6 and 1 2 months, patients underwent a structured clinical examination of sensation, muscle strength and reflexes and a neurophysiological assessment of motor nerve conduction velocity, sensory nerve action potential and heat and cold thresholds in upper and lower limbs. The placebo group tended to deteriorate whereas the active group showed progressive improvement. On every clinical and neurophysiological assessment except for the hot thresholds, EFO was significantly better than placebo. Patients with starting HbAlC levels below 10.0% did significantly better than those with levels above this. GLA as EPO offers considerable promise as an entirely new approach to the treatment of diabetic neuropathy.

Aldose Reductase Inhibitor (ARI) Treatment Normalizes Axo-glial Dysjunction and Improves Nerve Fiber Pathology in Advanced Diabetic Neuropathy

DA Greene, AAF Sima Ann Arbor MI

Twenty seven patients with prolonged (~18 years) diabetes and advanced diabetic neuropathy (sural nerve myelinated fiber density ~ 1800-2000/mm2) underwent sural nerve bropsies after 35.5 yearrs of treatment with the non-hydento in ARI tofrestat 200-400 mgld, which reduces sural nerve sorbitol by ~60 % (EASD # 321, A92, 90). Biopsies were compared to those from 62 untreated diabetic neuropathic patients, and to specimens from 19 non-diabetic control subjects (corrected for age and/or diabetes duration). In contrast to untreated neuropathic patients, tolrestat-treated patients exhibited normal axoglial dysjunction, characteristically increased by diabetic neuropathy in both man & laboratory animals, and a normal frequency of segmental demyelination. Tolrestat ireated patients also exhibited a 5-fold increase in nerve fiber regeneration, and (when corrected for



regenerating fibers) a marked increase in ihe percentage of structurally normal nerve fibers compared to the untreated neuropathic patients. Nerve fiber regeneration and the reduction in axo-glial dysjunction correlated positvely with the duration of tolrestat treatment. Tolrestat-treated IDDM and NIDDM patients exhibited 50°l° and 70% reductions in axonal atrophy and Wallerian degneration, lesions characteristic of diabetic neuropathy in IDDM and NIDDM patients respectively. The index of normality and measure of the density of structurally normal nerve fibers which correlates with nerve conduction velocity and clinically-detectable sensory deficits, was improved in tolrestai treated patients.

Conclusion: Prolonged treatmentwith tolrestat, a safe non-hydantoin ARI, improves clinically relevant parameters of nerve fiber pathology in diabetic patients with advanced neuropathy.

Effects of an Aldose Reductase Inhibitor on Central and Peripheral Nervous Conduction in Diabetic Polyneuropathy

J.M.A. Van Gerven, J.G. Van Drjk and H.H.P.J. Lemkes. Leiden, The Netherlands

Changes in conduction of the peripheral and central nervous system were studied in patients with diabetic polyneuropathy during 6 months treatment with placebo (n=16) or with the aldose reductase inhibitor tolrestat (200 mg 1 x d.d.) (n=20).

Conduction of the median nerve from wrist to Erb's point improved during tolrestat and deteriorated during placebo (-0.2 ± 0.3 mses vs 0.2 ± O.d msec (M ± SD), $p < 0.01$). ln patients where this was repeatedly measurable, the conduction latency of the tibial nerve from ankle to knee improved during tolrestat and deteriorated during placebo (-0.6 ± 0.7 msec vs 0.5 ± 0.4 msec, $p<0.05$). More tibial responses disappeared during placebo than during tolrestat (7/i6 vs 2120) and more responses reappeared during tolrestat than during placebo (5/20vs 1/16) ($p<0.05$). Central

(N 14-N20-interwave latency) and proximal peripheral nervous conduction were not influenced by treatment.
The spontaneous changes in HbAi that occurred during the study were proportionally related with concomitant changes in central conduction latency, in both groups (0.2 msecJ % HbA~). This association was unaffected by tolrestat. Thus, tolrestat treatrr~ent for six months improved peripheral nervous conduction. Changes in central nervous conduction that occurred during the trial were directly propartional to concomitant spontaneous glycemic changes. This association was not influenced by tolrestat.
COMPLICATIONS-RETfNOPATHY
Photographic retinal screening of a district diabetic population: a practical possibility?
Paul L. Drury, Dorothy Trump, J. Dowler, P. Marsden, R. Leng & J.S. Shilling
Greenwich, London, England.
There are few data on photographic retinal screening of district populations and the yield of previously undetected eye disease.
In 3 years (Aug'87-July'90) we have screened 1853 diabetic patients using a standard camera with mydriasis and Polaroid film. One morning session weekly was used for most of this period. These 1853 represent 61% of our known district register (3034 patients in a population of ca.210,000) and about 75°/ of those not already under ophthalmological care. Screening rates where highest, 65-70 %, for age groups 40-70 yrs with lower rates (45-50%) below age 40 and above 80 ($p<0.01$ ). Referral for a specialist eye opinion, judged necessary by a consultant ophthalmologist, was necessary in 229 patients at first screening (12.4%). This rate showed a marked correlation with age group, from less than 5 /° below 30 yrs to 20 / above 80 yrs ($p<0.01$ ). 58% of all referrals were aged 60 or more.
We conclude: (1) screening of a district population is both practicable and possible; (2) two sessions weekly·would allow complete coverage of this population once in 2 years; (3) eye disease found on screening is commoner in elderly patients.
Microalbuminuria and High Norma! Blood Pressure Predicts Development of Diabetic Retinopathy in Insulin Dependent Diabetic Patients
Mana Beatriz S. Freire, Pedro P. Bonomo, Aparecido B. Perena. Maria Tereza Zanella
Sao Paulo, Escola Paulista de Medicina, Brazil.
In order evaluate the relationship between urinary albumin excretion, arterial blood pressure and diabetic retinopathy in insulin dependeni we examined 55 patients without clinical proteinuria and whose disease had started before the age of 30. Each patient was asked to collect at least one overnight timed urine sample for albumin analysis by an ELISA method. Norrnolbuminuria was defined as urinary albumin excretion (UAE) of < 20 pg/min (n=32) and microalbuminuria as 21-200 pg/min (n =23). Patients with mi croalbuminuria showed higher levels of blood pressure, serum creatinine and glicosylated haemoglobin as compared to normoalbuminuric patients. Significant correlation was observed between diastolic blood pressure and UAE ($r = 0.52$; $p < 0.001$). Preprolife rative 8 proliferative diabetic retinopathy detected in 9 patients (16.4 % ). All of them had diabetes for more than 10 years, elevated UAE and diastolic blood pressure equal or higher than 85 mmNg. In our population of insulin dependent diabetics we found a high prevalence of microalbuminuria which is considered to be predictive of the laiter devefopment of diabetic nephropathy. Microalbuminuria is associated with elevated blood pressure and diabetic retinal lessions. We conclude that urinary albumin excretion should be monitored in patients with insulin dependent diabetes to detect those who should be considered at risk of developing nephropathy and retinopathy.
Early Treatment Diabetic Retinopathy Study (ETDRS) Effects of Aspirin Treatment on Diabetic Retinopathy
ETDRS Research Group, Bethesda Md.
Aspirin treatment did not alter the course of diabetic retinopathy in patients enrolled in the ETDRS. In this randomized clinical trial, 3711 patients with rnild to severe nonproliferative retinopathy or early proliferative diabetic retinopathy were assigned randomly to either aspirin (650 mg per day) or placebo. The relative risk of developing high-risk proliferative retinoparhy in eyes assigned to deferral in patients assigned to aspirin (N = 1856) compared with patients assigned to placebo N = 1855) was 0.97 with a 99 % confidence interval of 0.85 to 1 .11 The 5 year rate of moderate visual loss in eyes assigned to deferral was 26% in patients assigned to aspirin compared with 27 % in patients assigned to placebo. The relative risk of vitreous of pre-retinal hemorrhage in eyes assigned to deferral for patients assigned to aspirin compared with patients assigned to placebo was 1.05 (99°/ confidence interval, 0.81 to 1.36). Aspirin did not prevent the development of high-risk proliferative retinopathy and did not reduce the risk of visual loss, nor did it increase the risk of vitreous hemorrhage. The results indicate that for patients with stages of retinopathy studied in ETDRS diabetic retinopathy, aspirin is likely to have no clinically important beneficial effects on the progression of retinopathy. The data also show that 650 mg per day had no clinically


important harmful ocular effects for diabetic patients with retinopathy. These findings suggest there are no ocular contraindications to aspirin when requiredforcardiovasculardiseaseorothermedical indications.
Early Treatment Diabetic Retinopathy Study (ETDRS) Early Photocoagulation for Diabetic Retinopathy
ETDRS Research Group, Bethesda Md.
The ETDRS enrolled 3711 patients with mild to severe nonproliferative or early proliferative diabetic retinopathy in both eyes. One eye of each patient was randomly assigned to early photocoagulation and the other to deferral of photocoagulation. This early treatment, compared with deferral of photocoagulation, was associated with a small reduction in the incidence of severe visual loss but 5-year rates were low in both the early treatm,ent and deferral groups (2.6% and 3.7%, respectively). The relative risk of severe visual loss in eyes assigned to early photocoagulation compared with eyes assigned to deferral of photocoagulation was 0.77, with a 99% confidence interval of 0.56 to 1 .06. Both the severity of retinopathy and presence of macular edema at baseline were associated with the development of severe visual loss. For each of the three retinopathy categories defined on the basis of preliminary grading of fundus photographs and fluorescein angiograms, early treatment strategies varied. Analyses demonstrated no statistically significant differences between any of the early treatment strategies and deferral within each retinopathy

category. Adverse effects of scatter photocoagulation on visual acuity and visual field were also observed. Provided careful follow-up can be maintained, scatter photocoagulation is not recommended for eyes with mild or moderate nonproliferative diabetic retinopathy. When retinopathy is more severe, scatter phetocoagulation should be considered and usually should not be delayed if the eye has reached the high- risk proliferative stage.

COMPLICATIONS-GENERAL& MISCELLANEOUS

The New Therapeutics of Diabetic Foot-Report of 262 cases

Li shi ming, Hu Chao ping Beijing, China.

Anisodamine (654-2) is a kind of anticholinergic. Its main pharmacological effects include relaxing vasopasm improving microcirculation and promoting tissue regeneration. The former researches had confirmed the basic pathological changes of diabetic foot (DF) involve the angiostenosis, destruction of capillarybed and microcir-culationary disorder. Through a greot deal of clinical observation, the authors found that the new method of improving microcirculation with 654-2 can be used to treat the DF and get rather satisfactory result. The 262 cases with DF had undergone the hospitalized treatment with 654-2 during eight years therapeutics is a comprehensive method. The patients received 6544-2 either by daily oral or intravenous at doses of 0.5-1 .5 mg/kg/day, or by daily hydropathic compress on the wounds. Some of their wounds should be treated with surgical care and antiinfection. After receiving the new therapeutics with 654- 2, 83.2 % of the patients were healed completely, 9.8 % improved, 2.3% ineffective, 2.3% amputated, 2.3% died of cardiac, cerebrovascular and renal complication. The average healing time is 50 days. We primarily consider that this new etiological therapy of improving microcirculation have a higher cure rate and lower amputation rate for the patient with DF than it had. We hope the new therepeutics can open a shortcut for the treatment of DF.

Diabetic hand syndrome: association between flexor tenosynovitis and carpal tunnel syndrome and linkage with peripheral neuropathy and retinopathy

D. Jacques, E. Renard, J.L. Poirier, M. Chammas, C. JaNiol, J. Mirouze

Montpellier, France.

Diabetic hand syndrome comprises various entities including limited joint mobility (LMJ), flexor tenosynovitis (FT), carpal tunnel syndrome (CTS) and Dupuytren's contracture (DC), whose pathophysiology remains unclear. 56 diabetic patients, 20-70 years old, 23 insulindependent and 33 non insulindependent, attending diabetic clinics over 3 months, were clinically investigated for hand abnormalities in combination with hemoglobin AI, blood lipids, blood pressure, alcohol and tobacco use, diabetic complications assessments. Nerve conduction velocity up and down the wrists and transcutaneous oxymetry in the first dorsal intermetacarpal space were measured. Prevalence of hand lesions is in accordance with previous studies: 35% LJM, 20%TS, 12% CTS and 29% DC. A significant association is found between FT and CTS ($p < 0.05$). Whereas LJM and DC are linked with higher age ($p < 0.05$) independently of diabetic complications, FT and CTS are associted with peripheral neuropathy and, respectively, proliferative and all type retinopathy ($p< 0.05$). Transcutaneous oxymetry is not impaired and other parameters are not different whatever the hand fesions. The role of microvascular and peripheral nerve alterations could be suggested in the pathogenesis of FT and CTS although the mechanisms of their implication is not elucidated. In clinical practice, diabetic patients claiming for hand symptoms should undergo careful analysis owing to the specific treatments of FT and CTS.

Abnormalities of haemostasis in Type 2 diabetes with microalbuminuria

A Collier, A Rumley, JP Leach, GDO Lowe, M. Small, Glasgow, Scotland.

Microalbuminuria is a predictor of increased mortality in Type 2 diabetes, and this appears to be primarily due to cardiovascular disease. Abnormalities in haemostasis have been implicated in the development of diabetic vascufar disease. The aim of this study was to investigate markers of coagulation (Fibrinogen, von Willebrand factor (vWf) and fibrinolysis [plasminogen-activator inhibiter (PAI) tissue plasminogen activitor (tPA) and Be»42 (in vivo indicator of plasmin activity)] in Type 2 diabetic patients (aged 45-65 yrs) with microalbumin.uria (n=1 2) and normal urinary albumin exeretion (n=12) plus 12 comparable non-diabetic control subjects. Except for Bsi~az, all the haemostatic factors were increased ($p<0.05$) in the diabetic patients compared with control subjects. The microalbuminuric diabetic patients had further increased levels of tPA ($p<0.02$) and vWf ($p<0.03$) compared with patients without microalbuminuria. These results suggest an activation of the haemostatic balance favouring a hypercoagulable state in Type 2 diabetes which may contribute to the increase in cardiovascular mortality seen in patients with microal-buminuria.

Increased Apo(a) Levels in IDDM patients with Microalbuminuria

A.J Jenkins, J.S. Steele, E.D. Janus, J.D. Best

Melbourne, Australia

IDDM patients with raised urinary albumin excretion have a greatly increased risk of macrovascular disease. The elevated total cholesterol, triglyceride, low HDL, higher blood pressure and fibrinogen levels may not account for all the vascular disease excess.

lNTNL. J. DIAB. DEV. COUNTRIES (i991), VOL. 1 i 35

We examined apo(a) levels in 101 IDDM patients with different levels of urinary albumin exeretion, and compared them with levels in 107 non-diabetic controls and 40 male coronary artery graft patien2s (CAG). Apo(a) is the plasminogen like apoprotein of the highly atherogenic lipoprotein (a). Apo(a) levels were increased in IDDM patients with microalbuminuria (mean apo(a) 487 UlL) and a1buminuria (mean 396 ulL) to levels not ditferent from those of the CAG group (mean 366 U/L), which were higher than those of the controls (mean 242 U/L, $p = 0.017$). Apo (a) levefs in fDDM patients without microalbuminuria (mean 182 uJL) were significantly less than in those with microalbuminuria ( $p = 0.001$) and with albuminuria ($p = 0{,}020$), but did not differ from controls. Apo(a) levels were not related to age, gender, duration of diabetes, glycaemic control, body mass index, insulin dose, totaf cholesterol, trigylyceride or HDL. The 27 IDDM patients who had required laser treatment had higher apo(a) levels than those who had not (mean apo(a))555 vs 207, $p = 0.002$) This may reflect the relationship between diabetic kidney and eye disease. We suggest raised apo(a) levels may contribute to the recognised heightened vascular disease risk of IDDM patients with inereased urinary albumin loss. The

causeleffect relarionship between raised apo(a) and urinary albumin loss requires further evaluation.

Glycemic Control and Diabetic Complications in Patients with Type 2 (non Insulin Dependent) Diabetes

P. Lazzari, G. Brunelli, L. Boari, Cremona. Italy,

In order to evaluate the influence of glycemic control on the development ot coronary heart disease (CHD), nephropathy (N) and retinopathy (R), we studied 514 type 2 diabetics (226 M, 228 F, age 63.5±8.3 yr). On the whole, 21.1% had CHD, 7.7 % N, and 13.2% R. Glycemic control was evaluated by average daily glycemia (ADG) (mg/dl) ~onsidering the fasting values of the last 10 years. Stratifying ADG (< 100;101-150;151-200;>200), CHD and N were more frequent respectively when ADG~l5O than when < 150 (26.1°/ vs 18.2% p<0.05) and when ADG>200 than when S 200 (30.0% vs 6.9. %, p<0.01 ), whereas the prevalence of R was similar in all strata (1 1.1%; 11 .5%; 16.3°/ ; 10.0%) whose duration of diabetes was comparable. ADG was similar in hypertensive and normotensives, as well as the duration of diabetes; CHD was more frequent in the former than in the latter (25.4% vs10.6%, p<0,001 ), whereas the frequency of N and R was similar in the 2 groups (8.2% vs 6.5% and 13.1% vs 13.3%). ADG was higher in insulin-treated than in non insulin-treated patients (i60.6± 25.1 vs 138.6 ± 21.8,p<0.0001) as wefl as the duration of diabetes; R was more frequent in the first then in the second (26.7% vs 10.7%, p<0.001), whereas the prevalence of N and CHD was similar in the 2 groups (9.4% vs 7.4% and 26.7% vs 20.0%). The study suggests a wide variation regarding the reiationship between the degree of glycemic control and the onset the diabetic complications, underlying at the same time the role of hypertension as risk tactor for CHD and indicating that the coexistence of a longer and more severe disease (worse glycemic control and insulin therapy) may not be an obligatory prerequisite for the development of vascular damage.

Risk Factors for Late Complications of Insulin Dependent Diabetes MeNitus

Gertrud Kacerovsky-8ielesz, W, Grossmann and H. Hohenecker Vienna Austria.

The aim of the study was to estimate the risk of late complications (I.c). based on glucose control (as monitored by HbAic levels obtained in longitudinal manner) age and duration of diabetes (d.o.d.). 171 patients were examined: mean (m) age of onsei (a.o.o.) 26.3 f 12.1 (range 1-54) d.o.d. 14.8 ± 11.1 (all trained, using self-control,

attending outpatients clinic four times a year, c-peptid neg., HLAtyped). Testing of groups with various HbAtc levels showed an 8°/ HbAlc level to be the best discrimination, Therefore two groups were formed, over and under 8°/ HbAi c. The time spent in one group was also taken into account. Statistical methods are analysis of variance, non parametic tests, survival analysis, log. regression.

It showed that the d.o.d., particularly in retinopathy (r.) the a.o.o. and the leve! and length of time spent in a group have an important effect on the development of I.c. Onset before age of 12 indicates delayed l.c. A patient suffering from diabetes for 10 years and with a level over 8% HbA 1c fora longerperiod is twice as likely to develop r. as a similar patientwith a level under 8% HbAlc (rel. odds: 2.28). Under the same conditions neuropaihy is 90 % more likely (rel odds = 1 .89) with a level over 8% HbAlc. Only i6 patients suffer from nephropathy making it impossible to calculate the risk.

There is a positive significant correlation between HbAlc leveis 20%-30% above normal and duration of high level. It depends on a.o.o. and d.o.d. Using these facts. It sesms possible to estimate the risk of late complications at any stage of the iflness.

lnsulin as a Risk Factor for Diabetes Complications

S.A. Ross and G.H. Fick University of Calgary, Alberta

Ideal glucose control is considered important in preventing the development and progression of diabetes complications (DC).

Exogenous insulin is esseniiaf for the survival of the type I diabetic and is adjusted to help maintain good glucose control. Many type II diabetic subjects, however, will also receive insulin as part of their treatment due to the poor glucose control achieved from diet or tablets. It is assumed that the addition of insulin in the type 11 subjeet, will help prevent longterm DC. Yet insulin itself may be a risk factor for DC in scme individuals. As part of a major epidemiologic study of diabetic retinopathy in Southern Alberta, 2300 insulin using (IU) and 1400 non-insulin using subjects (NON IU) were assessed. DR was measured by stereo-fundal photographs utilizing the Airlie House Classification. Glucose control was measured by HbAlC. To determine endogenous insulin production, C-peptide (CP) was measured by radioimmunoassay in 1U subjects. Those with CP < 0.5 nmfl were considered to be insulin dependent (I DDM). Those with CP> 0.5 were considered to be type 11 subjects on insulin (IIIIU). As the progression of DR can be affected by glucose control, it must be considered a confounding factor, thus, DR was assessed after adjusting for glucose contral. On the basis of H8AIC, the subjects were divided into 3 groups of glucose control-perfect, satisfactory and poor controf. DR was then assessed at 3 levels of severity based on retinal. photographs- nil, moderate and severe DR. At all ranges of glucose control, the prevalence of DR was significantly greater in IIfIU compared to NON IU subjects (p < 0.001). To illustrate the differences between IIlIU and-NON 1U subjects, even with the poorest glucose control, the difference in DR prevalence persists-lDDM 35%, IIfIU 34°l°, NON IU t i% ( p < 0.0001 ) There were no significant differences between IDDM and IfllU. Controlling for other risk factors such as duration, hypertension and hyperlipidemia, the same ditterences persist between IIIIU and NONlIU. These data indicates that regardless of glucose control, the use of insulin in II/IU is a major risk factor for DR placing the IUlU at the same risk as an IDDM subject. Thus insulin use should be carefully considered in the II/IU diabetic subject.

3& lN7-NL. J. DIAB. DEV. COUNTRIES (J99J), VOL. J J

Plasma prorenin versus 24h albumin excretion for monitoring micro-vascular disease in type 1 diabetes mellitus

P.J. Blankestyn, FHMDerkx, RFA Weber, JC Birkenhagerand Madh, Schalekamp

Rotterdam, the Netherlands.

Albuminuria (Ualb) is used as a marker of micro angiopathy. The day-to-day Ualb excretion varies considerably and this large intra-individual coefficient of variation (CV) makes interpretation difficult and repeated measurements are therefore advised. Plasma prorenin but not renin is abnormally high in patients with diabetes mellitus (DM) complicated by micro- vascular disease. In this study of 62 type 1 DM patients (35 male, mean age 36 yr, range 18-64,

mean duration of DM 17 yr. range 2-42) with normal serum creatinine (<110 umol/L) treated only with insulin, 24h Ualb was measured 3 times with an interval of 4 weeks. On the sarne day blood was collected in supine position after 30 rnin of bedrest for plasma prorenin and other hormonal measurements. The Ualb was 13 mg/24h (median, range 3-632) and prorenin 185 mU/L (median, range 93-1917). There was a significant correlation between Ualb and prorenin ($r=0.54$, $p<0.001$ ). The intra-individual CV of Ualb was 27 % (median, range 1-130) and of prorenin 7% (median, range 1-37) ($p<0.001$). No correlation was found between prorenin and age, duration of DM, renin, noradrenaline, adrenaline, dopamine, urinary Na and urea excretion, blood pressure, g3ornerular filtration rate and renal plasma flow (125 iothalamate and -hippuran clearance resp) or HbAlc.

This study supports the vic:w that prorenin is a marker of microangiopathy. Prorenin measurements have sorne advantages to Ualb low intra-individual coetficient of variation and no urine colleciions are needed.

Capillary Basement Membrane Thickness and its Relationship to Glucose Control, Hypertension, and Lipids

S. Palushock, V K. Bahl, N. Patel, S. Doshi, H. Yamakawa, and WM. Mook

Pittsburgh, PA.

Thirty patients were enrolled in a protocol to study the natural history of capillary basementmembrane thickness (CBMT) in Type I Diabetes Mellitus and its relationship to glucose control, blood pressure, and lipids. The study duration was nine years. Eighteen patients completed the study period i.e. eight female and ten male. The average age was 23 ± 9.4 years and the average duration of diabetes at the time of enrollment was 6.5 ± 4.8 years. All patients were placed on intensive insulin therapy at the beginning of the study. A needle biopsy of the quadriceps muscle was performed yearly and the mean CBMT was measured. Every three months glycosylated hemoglobin Alc, lipid fractions, and blood pressure were obtained and the mean HbAlc was reported. Despite improved control of the diabetes, the CBMT values progressively increased over the first five years. However with further improvement in blood sugar control between the 6th and 9th year, the CBMT did not show any further rise, and indeed CBMT decreased significantly as blood sugar control was nearly normalized (HbAlc less than 8.6%) at the 8th and 9th years of the study. No significant association was found between CBMT and lipid levels, or systolic and diastolic blood pressure. It appears near normal control of blood sugars, independent of lipids and blood pressure is the main determinant of progression.

Use of New Inhibitor of Aldose Reductase, Isodibut, for Treatment of Diabetic Complications

A.S. Yefimov", I.M Melnik, N.D. Tronko, B.N. Mankovsky, E.K. Yelimova, A.l. Danilova, P.M. Karadun, S.T Zubkova, and V.G. Naumenko

Kiev UkSSR.

Isodibut is an inhibitor of aldose reductase. In experiments with streptozotocin induced diabetic rats the decrease in the aldose reductase activity of sciatic nerve, lens and aorta resulting in the reduction of sorbitol content under isodibuteffect has been shown. Clinical trials of the drug in 47 patients at the age ot 16-50 with different duration of type 1 & type 2 diabetes mellitus have been revealed the positive effect developing the decrease in the signs of diabetic neuropathy (peripheral and central). The improvement of vascular microcirculation of lower extremities (in 40.9 % patients) and eye fundus in the patients with preproliferative diabetic retinopathy has been observed. Studing the brain funetional status under isodibut effect by electroen-cephalography with automatic frequency integral analysis and by method of visual evoked potentials the normalization of the ratio in basic rhythms of encephalograms, the decrease in peak latency of some components of visual evoked potentials have been noted. The positive effect of this drug on acetylcholinesterase and K, Na-ATPase activity in erythrocytes of the patients has been shown.

The Treatment of choice for Erectile Impotence

William D. Alexander Sidcup. Kent, UK.

Patient awareness ot impotence treatrnents has increased but availability needs to impreve. We have been running a feasibility study to determine whether a physician can provide a male erectile impotence assessment and treatment service, including general eounselling, vacuum devices, papaverine self-injection therapy or refierral to a urologist for a prosthesis if non- surgical methods fail. This has proved successful and is now a routine part of our diabetes care service. We presentresults regarding treatmentoutcomes preference and patient characteristics of our first year experience, 29~32 patients (91 % ) who desired physical treatments preferred to try intracorporeal papaverine self injection therapy after discussion and demonstration of all options. The characteristics of this group were compared with those of 36 patients who decided they would rather accept their impotence problem. Mean age of the treatment group was 50 vs 63 years; 66 % were insulin treated vs 22 %; clinically assessed aetiology was predominantly neuropathic in 72 % vs 19 % , psychological 41°% vs 36% and vascular 1 7% vs 39 %. 80 % had volunteered their problem vs 22% of the untreated group, the majority of whom had responded to a questionnaire. At follow up (>6 months )-16 continue to self inject, 7 have stopped treatment, 4 have been referred for prostheses, 2 use Erecaidvacuum device. In conclusion physicians can successfully run an impotence treatment service and should include it in their diabetes care programme to improve availability of treatment to patients. Intracorporeal injection of vasoactive drugs is the treatment of choice fer younger, insulin treated patients with neuropatlric psychological impotence who volunteer this problem. Older NIDDMs have more complex problems and ;ess often request or require physical treatments.

lNTNL, J. DIAB. DEV. COUNTRIES (1991), VOL. 11

## DIABETES & PREGNANCY

A study of Factors Influencing Pregnancies Associated with Glucose Intolerance

G.V. Krishnaswami, G. Vijaya Kumar, JR. Subramaniam, M. Chellamariappan, P. V. Ashabai, K. Balamurugan, P. Krishnaswami, M. Dhamy'a, S. Fernando, Vijayalakshmi, V Prasad, B. Subramanyam, S. Suresh

Madras, india.

Out of 947 deliveries in the past 18 months, 33 pregnancies were studied with regard to the nature of glucose tolerance, therapeutic requirements, metabolic control, obstetric history, timing and mode of delivery. 19 cases (57%) had overt diabetes and 14 cases (43%) had Abnormal glucose tolerance. 68% had bad obstetric history. 10 cases had diabetes prior to conception (6 IDDM and 4 NIDDM) and they required insulin. In the remaining 23 cases only 3 (13%

required insulin; the rest were on diet only, Metabolic control during pregnancy was monitored using blood glucose, GHb, fructosamine and 24 hour profiles. All of them were given Pyridoxine 80 mg daily till delivery. There was good correlation between mean blood glucose 145 mg% (SD 45.05). GHb 9.01 % (SD 1.38) and fructosamine 2.51 (SD 0.57). 6 cases had hydramnios and equal number had pre eclampsia. The mean gestational age at delivery was 38.2 week, (SD 1.63). 22% delivered vaginally and 78 % by LSCS. 9% had successful outcome. Average birth weight was 3.28 Kgs (SD 0.56). None in this group had congenital anomalies as compared with 2.3% of anomalies seen in 914 non diabetic deliveries. Under our conditions successful outcome of diabetic pregnancies depend on metabolic and obstetric factors., timing and mode of delivery being of utmost significance after foetal maturity. In our experience IUDs are more frequent than congenital anomalies in offsprings of diabetic and pre diabetic mothers. Our study has posed important questi0ns to the accepted theories in the management of diabetic pregnancies.

SOCIAL ASPECTS OF DIABETES MELLITUS

The Epidemic of Indian Childhood Diabetes in Leicester: Social Cultural Differences between Cases and Control Population

M. Boddington and A.C. Burden Leicester, UK

We have provided evidence in favour of an epidemic of childhood onset (<15 years) insulin dependent diabetes in Indian children resident in Leicester, UK. These children either come from, or their forefathers came from, the Indian Subcontinent. The present work examines the hypothesis that the amount of cultural adaption to English life is greater than their non-diabetic peer.

A trained Diabetes Specialist Health Visitor visited each family with a structured questionnaire; to enquire when the diabetes started, where they had lived previously, schooling, friends, dietand living condifsons.

26 patients were contacted of the 34; these families have been compared to the Leicester City Indian Census population. They are more likely to have been born in the United Kingdom; to eat meat; to live in detached or semi-detached housing; to live in an area with few other Indians.

The preliminary results suggest that Indian children are more culturally Anglicized than non-diabetiCs; a case control study is urgently required to verify this.

PATIENT EDUCATION

Feasibility of lnsulin Therapy in NIDDM: Results from a Finnish Multicenter Study

M. Heikkila, L. Flink, L. Hyvarinen, J. Jakala, M. Kalkkila, A. Karjalainen, M.L. Kekalainen, R. Nopola

Finland

150 patients with NIDDM (age 59± 1 yrs. BMI 28± 1 kg/m2, HbAtc 9.8± 0.1 %) and treatment failure were randomized for 3 months in 5 goups in 6 centers: MOR/EVE + OA (NPH at 7 a.m.l9 p.m. + oral agents), 2-INJ (NPH + regular at 7 a.m. and 9 p.m.), MULT (NPH at 9 p.m. + 3 x regular), CONT (oral agents). AT O and 3 months, attitudes and knowledge were evaluated using detailed questionnaires. Each center used a similar teaching program, and all patients visited a teaching nurse and doctor at -6,-3,0,2,4,8 and 12 weeks.

Knowledge 0 monthsa 3a months

Definition of normoglycemia 96% 100 % Identification of carbohydrates 77% 75°.~ Identification of fats 90 % 88% Worst complication in NIODM 45% 45% Effect of exercise on glucose 99°l0 100 %

Attitudes after 3 months Easierb Similarb Moreb diffic.

In)2Ctlng mSUlln 81% 18% 1% Home glucose monitoring 68% 31°/ 1% DIetCOmpIIdnC2 44% 21% 37% a % correct answers, b than assumed before study

MOR EVE 2-INJ MllLT CONT +OA +OA

Change in HbAlc -1.8' -1.9" -1.5 -1.9" -0.5

Wellbeing Improved 87% 100°fo' 95%' 70°fo' 53°!0

Willing to continue 100% 100% 100% 90%

Insulin `p<0.05, "p<0.01 vs CONT

We conclude that most patients with NIDDM know enough to start insulin therapy and find the therapy easier than they expect. Improvement in subjective wellbeing is significantly associated with insulin therapy.