Clinical Science and Molecular Medicine (1978) **55**, 1P–31P

MEDICAL RESEARCH SOCIETY

A meeting of the Medical Research Society was held on 7 and 8 July 1978 at the University of Sheffield. The following Communications were presented.

Communications

1. EVOLUTION AND PREDICTION OF INFARCT SIZE AFTER ACUTE MYOCARDIAL INFARCTION IN MAN

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The evolution and size of acute myocardial infarction (MI) was studied in 41 patients by using 35 lead praecordial maps and serial MB CPK levels after extensive reproducibility studies in 18 normal subjects and five patients.

Maximum R wave loss and Q wave development occurred from 4 to 60 h after the onset of pain with mean values of 23 ± 12 h and 23 ± 12 h respectively. R loss and Q development were 57% and 43% of final value at 6 h, 67% and 64% at 12 h, 86% and 91% at 24 h, 90% and 95% at 36 h and 98% and 99% at 48 h respectively. This contrasts with earlier reports that loss of regional electrically viable myocardium is complete in 6 h.

Three patterns were observed. The first group showed a rapid loss of R waves (mean 9 h: range 4–14 h) with a rapid fall of high initial ST segment elevation. The second group demonstrated a gradual R loss (mean 33 h, range 14–48 h) with a moderate ST segment elevation persisting longer. In the third group, ST re-elevation preceded reinfarction.

Correlation of maximum ST elevation and maximum Q waves with total enzyme release was highly significant ($r = 0{\cdot}681$, $P < 0{\cdot}001$; $r = 0{\cdot}945$, $P < 0{\cdot}001$ respectively). Maximum ST segment elevation predicted final Q wave development ($r = 0{\cdot}723$, $P < 0{\cdot}001$) at a time when infarction was not complete.

In four patients increase in S waves accompanied R wave loss; QS waves developing only after complete R loss occurred. The duration of ECG changes and evolution pattern were independent of infarct size.

The significance of measuring all the waves in the ECG has been demonstrated. Knowledge of the time course of infarct size evolution and the relationship between maximum ST segment elevation and maximum Q wave changes can be used to assess the efficacy of interventions designed to limit infarct size.

2. THE EFFECT OF MONITORED SUB-ERYTHEMAL DOSES OF ULTRAVIOLET RADIATION ON PLASMA 25-HYDROXYCHOLECALCIFEROL IN LONG-STAY GERIATRIC PATIENTS

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Plasma 25-hydroxycholecalciferol [$25(OH)D_3$] is frequently low or undetectable in long-stay geriatric patients (Corless, Beer, Boucher, Gupta & Cohen. 1975, *Lancet*, **i**, 1404–1406), due to a combination of poor dietary intake and malabsorption of vitamin D (Barragry, France, Corless, Gupta, Switala, Boucher & Cohen, 1975, *Clinical Science and Molecular Medicine*, **54**, 28P) and to poor or negligible exposure to ultraviolet (u.v.) radiation. The day rooms of two long-stay geriatric wards were illuminated for periods during the day with Westinghouse FS20 strip lights, providing u.v. radiation covering the u.v. spectrum of sunlight but extending to somewhat shorter wavelengths (minimum 254 nm). The patients in the wards were divided into four groups, each group receiving u.v. radiation from two to eight strip lights during their timed daily period in the day room over a total time of 8 weeks; control groups receiving no u.v. radiation were also included. The face, lower arms and legs were exposed. Exposure to u.v. was monitored by using polysulphone badges (Challoner, Corless, Davis, Deane, Diffey, Gupta & Magnus, 1976, *Clinical and Experimental Dermatology*, **1**, 175–179) worn by each patient and varied from 0·36 ± SEM 0·14 mJ/cm² per week in the control groups to 24·9 ± 1·90 mJ/cm² per week in the highest dose group. The data provides the first quantitive study of the u.v. radiation dose–response relationship in terms of plasma $25(OH)D_3$ in human subjects. Plasma $25(OH)D_3$ rose by the end of the 8 weeks period by 28·05 ± 5·98 nmol/l in the group receiving a mean of 13·6 ± 0·53 mJ/cm² per week and doses larger than this had no greater effect at this time. In no group was the u.v. radiation sufficient to produce erythema. Administration of u.v. radiation in this manner may be the most convenient way of preventing and treating vitamin D deficiency in the elderly long-stay patient.

3. INDUCTION AND INHIBITION OF HEPATIC MICROSOMAL ENZYMES BY RIFAMPICIN AND ISONIAZID

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The antibiotic rifampicin is a powerful inducer of liver microsomal enzymes in man (Remmer, Schoene & Fleischmann, 1973, *Drug Metabolism and Disposition*, **1**, 224). We have shown elevated plasma levels of lysosomal enzymes during rifampicin and isoniazid therapy (W. Perry, M.V. Jenkins, Erooga & T. C. B. Stamp, 1978, *Biochemical Medicine*, In press). To determine further the metabolic effects of these drugs plasma half-lives of antipyrine and of quinine and urinary excretion of D-glucaric acid and 6β-hydroxycortisol were measured as indices of hepatic enzyme induction.

Plasma antipyrine half-life showed a mean fall of 31% in eight patients after receiving rifampicin and streptomycin for between 3 and 20 days (streptomycin is not known to affect liver microsomal enzymes and is excreted unchanged by the kidney). After isoniazid was substituted for streptomycin antipyrine half-lives repeated between 1 and 18 months during treatment showed a mean fall from pretreatment values of 34·6%. However, in three patients a partial inhibition of rifampicin induction by isoniazid was observed. There was a marked fall in quinine half-life in two patients tested and in one this change was inhibited by isoniazid. Serial antipyrine half-lives in four patients tested suggested a variable speed of induction.

During rifampicin and streptomycin treatment there was a simultaneous rise in urinary D-glucaric acid excretion which correlated inversely with decline in plasma antipyrine half-life ($r = -0{\cdot}761$, $P < 0{\cdot}05$). Subsequent introduction of isoniazid reversed this effect. Urinary 6β-hydroxycortisol was elevated in all eight patients and in three patients excretion was increased over tenfold.

Our findings show the inductive effect of rifampicin on four indices of microsomal enzyme activity and demonstrate the inhibiting properties of isoniazid on this induction. The variable percentage decrease of the antipyrine half-life after rifampicin

induction (13·7–62·6%) is similar to the effect of phenobarbitol (Vessel & Page, 1969, *Journal of Clinical Investigation*, **48,** 2202).

4. EFFECTS OF α- AND β-ADRENERGIC BLOCKADE ON THE CIRCADIAN RHYTHM OF BLOOD PRESSURE IN HYPERTENSIVE SUBJECTS

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The Oxford recording system has been used to monitor the blood pressure (B.P.) of hypertensive patients over long periods and thereby demonstrate the circadian rhythm. Features of importance include the nocturnal nadir occurring around 03.00 hours and a subsequent rise, rapidly accelerating at the time of waking. The rise in heart rate is generally delayed by 2–3 h behind that of BP. Modification of this rhythm by various β-adrenergic blockers has been studied when given according to conventional regimens. Neither oxprenolol given t.i.d. nor atenolol given once daily in the morning affected the early rise but atenolol given in the evening did reduce it at the expense of B.P. control in the afternoon. Metoprolol given b.i.d. appeared to reduce early morning B.P. but comparison of hourly mean B.P. in six patients before and during treatment with the drug did not achieve statistically significant differences ($P > 0{\cdot}05$) at this time. Heart rate, however, was significantly reduced throughout the 24 h period ($P < 0{\cdot}05$). The effects of giving an α-adrenergic blocking agent (Indoramin) at night were studied on eight patients and compared with their B.P. values on the previous night when no treatment had been given. Significant B.P. reduction occurred during the night but the slope of the early morning B.P. rise was unaltered. These findings may have important implications in the formulation of therapeutic regimens in the treatment of hypertension.

5. STUDIES ON FERRITIN IN MALIGNANT LYMPHOMA

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We have previously reported the finding of a factor in spleens involved by Hodgkin's disease to which other patients with malignant lymphoma may be sensitized in the leucocyte-migration test (Hancock *et al.*, 1976, *British Medical Journal*, **i,** 556, **ii,** 351). Such sensitization has not been demonstrated in studies on 26 patients with lymphoma with the lymphocyte transformation technique. Further studies with the leucocyte-migration test have shown (a) similar sensitization with foetal spleen and (b) that the original splenic factor is probably ferritin in a form different from that found in the normal spleen. Biochemical and immunological investigations using normal spleen ferritin and Hodgkin's spleen ferritin, together with respective antisera, confirm that there are differences between these ferritins. Elevated levels of plasma ferritin are found in malignant lymphoma by using Hodgkin's spleen ferritin antisera in immunoradiometric assay (May & Hancock, 1977, *Clinical Science and Molecular Medicine*, **53,** 14P); we have also found elevated levels of plasma ferritin with a commercial radioimmunoassay system (Travenol) using normal liver antiferritin but the values obtained have always been lower, in various ratios, than those found with our own system using Hodgkin's spleen antiferritin. Preliminary studies with isoelectric focusing suggest that the isoferritin profile of ferritin from Hodgkin's spleen differs from that of normal spleen, resembling that seen with foetal spleen.

6. INSULIN-INDEPENDENT DIABETES: DEFECTS IN THE REGULATION OF TWO ADIPOCYTE ENZYMES INVOLVED IN CARBOHYDRATE AND LIPID METABOLISM

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A major action of insulin is to maintain intracellular levels of enzymes involved in carbohydrate and lipid metabolism. The mechanism of this effect is obscure but may involve a stimulation of translational activity for synthesis of enzymes. We have previously reported that adipose tissue of obese diabetic subjects contains reduced activities of phosphofructokinase, which can be restored to normal by insulin therapy *in vivo* (Galton & Wilson, 1971, *Clinical Science*, **41,** 545). As a further measure of the 'resistance' of adipose tissue to the action of insulin on the maintenance of intracellular enzymes *in vivo* we have studied the activities of lipoprotein lipase and phosphofructokinase in a group of obese diabetic patients who have an increase in plasma insulin after an oral glucose load. The results are shown in Table 1.

Our results suggest that a failure of insulin to maintain activities of regulatory enzymes may be an important feature in

TABLE 1. *Activities of (a) lipoprotein lipase and (b) phosphofructokinase in obese diabetic patients showing increased plasma insulin concentration after oral glucose*

Patient group	*n*	Age (years)	Weight (kg)	Glucose (mmol/l)	Insulin (μunits/ml)		Adipose tissue enzymes (a) lipoprotein lipase (nmol $h^{-1}/10^{-6}$ cells)	
					0	1 h	Extracted	Released
Obese	12	43 ± 3·6	103 ± 6	4·4 ± 0·2	11·9 ± 1·8	66·1 ± 7·8	173 ± 41	191 ± 42
Obese diabetic	11	54 ± 2·8	81 ± 4	8·3 ± 1	21 ± 7	57 ± 14	105 ± 21	90 ± 22
P (vs obese)		<0·02	<0·05	<0·01	N.S.	NS	<0·02	<0·05
Obese hypertriglyceridaemic	9	47 ± 5	86 ± 6·4	4·3 ± 0·2	18·5 ± 3	103 ± 14	85 ± 15	70 ± 22
P (vs obese)		N.S.	<0·05	N.S.	<0·05	<0·05	0·03	<0·02
							(b) Phosphofructokinase (unit/unit of hexokinase)	
Obese	11	43 ± 4·5	97 ± 5	4·2 ± 0·7	18·7 ± 2	83 ± 9	0·88 ± 0·07	
Obese diabetic	12	44 ± 4	86 ± 5	9·7 ± 1·8	15·6 ± 0·8	57 ± 11	0·50 ± 0·09	
P (vs obese)		N.S.	N.S.	<0·01	N.S.	N.S.	<0·01	