MEDICAL RESEARCH SOCIETY

A meeting of the Medical Research Society was held on Friday and Saturday, 27 and 28 September 1974 at The Medical School, University of Birmingham, Edgbaston, Birmingham. The following Demonstrations and Communications were presented.

DEMONSTRATIONS

1. Isolation and properties of human glomerular basement membrane protein
   J. Wheeler, J. Holland and J. D. Blainey (M.R.C. Renal Research Laboratory)

2. Reactivity of vascular beds in slow and fast muscles
   W. Allum, Mary Cotter and Olga Hudlicka (Department of Physiology)

3. Formation of neuromuscular junctions in chick embryos
   Tessa Gordon and Greta Vrbova (Department of Physiology)

4. Central nervous pathways in cardiovascular control
   S. M. Hilton, R. M. McAllen and K. M. Spyer (Department of Physiology)

5. Neuropharmacological modification of neuronal processes in the visual cortex
   A. M. Sillito (Department of Physiology)

6. The measurement of human muscle tone
   R. M. H. Rack and H. F. Ross (Department of Physiology)

7. A gravimetric plethysmograph for clinical use
   C. D. Hill, J. R. Jackson and Jennifer Matthews (Department of Physiology)

8. A hybrid cardiovascular computer for bedside use
   J. R. Jackson (Department of Physiology)

9. The mode of action of furosemide ('Lasix'): investigations using in vitro frog (Rana temporaria) skin
   C. J. Lote (Department of Physiology)

10. Enzyme-based isotope derivitization assay techniques
    M. Mitchard and J. Andrews (Department of Therapeutics and Clinical Pharmacology)

11. Computer assisted drug prescribing
    L. Beelby, G. F. Walker and J. M. Bishop (Department of Therapeutics and Clinical Pharmacology and Department of Medicine)

12. A breathalyser technique for predicting drug induced changes in the rate of drug absorption
    M. J. Kendall, R. C. Hall, R. Carter and D. Brown (Department of Therapeutics and Clinical Pharmacology)

13. Estimation of thyroxine binding globulin concentration
    W. A. Burr and D. B. Ramsden (Department of Medicine)

14. Radioimmunoassay of tri-iodothyronine and thyroxine
    E. G. Black, S. Griffiths and R. Hoffenberg (Department of Medicine)

15. The measurement of total thyroxine in serum and urine by a simple protein binding technique
    J. F. Finucane (Department of Medicine)

16. On-line computer analysis of ventricular pressure recordings
    M. V. Forbes and P. Finnegam (Department of Medicine)

17. Methods for recording the flow volume diagram of a forced vital capacity manoeuvre
    S. R. Sales and A. C. Pincock (Department of Medicine)

18. Solenoid-operated valve box for oxygen breath tests
    H. A. Crist and K. D. Lee (Department of Medicine)

COMMUNICATIONS

1. URINARY CYCLIC AMP EXCRETION IN THYROID DISEASE
   D. J. Carter and D. A. Heath
   Department of Medicine, University of Birmingham
   (Introduced by R. Hoffenberg)

   A radioimmunoassay for urinary cyclic AMP has been developed with an antibody against cyclic AMP succinylated at the 2'O position. It has been applied to the study of twenty-two normocalcaemic patients with hyperthyroidism and nine normocalcaemic patients with hypothyroidism. Three hypothyroid patients with hypercalcaemia have also been studied. Urine has been collected under basal fasting conditions and during 24 h periods.

   Urinary cyclic AMP/creatinine ratios (pmoles/g creatinine excreted) are raised in the female hyperthyroid patients (mean 5.40, range 2.10-8.63) as compared with female controls (mean 3.52, range 1.88-5.96) and female normocalcaemic hypothyroid patients (mean 3.11, range 1.34-4.18).

   The total 24 h urine excretion of cyclic AMP (pmoles/24 h) has been found to be raised in both male and female hyperthyroid patients (males mean 5.47, range 2.54-8.90; males mean 7.54, range 5.88-9.33) as compared with controls (males mean 3.83, range 2.14-5.79; males mean 5.49, range 2.95-6.99) and hypothyroid patients (males mean 2.66, range 1.79-3.96; and males mean 1.86, range 1.63-2.10).

   A relatively low phosphate excretion index in the
hypothyroid patients (mean 0.06, range -0.13 to +0.03) supports the concept of relative hypoparathyroidism in hyperthyroidism. Thus it is unlikely that the increase in urinary cyclic AMP excretion in hyperthyroidism is derived from the renal cortex under stimulation of PTH.

Follow-up studies are in progress in the same patients after they have become euthyroid in response to treatment.

2. ALTERATIONS IN LIVER ADENYLATE CYCLASE RESPONSIVENESS DURING INDUCTION OF TUMOURS IN RAT LIVER WITH 3'-METHYL-4-DIMETHYLAMINOAZOBENZENE

Helen Boyd and T. J. Martin

Department of Pharmacology, University of Miami School of Medicine, and Department of Chemical Pathology, University of Sheffield

Amongst the hormonal changes associated with cancer some evidence has emerged of changes in cell surface hormone receptor specificity of certain tumours (Schort et al., 1971, Journal of Biological Chemistry, 246, 5806). The present experiments were designed to study the development of such changes during tumour induction.

Mature rats were fed a diet containing 0.06% of the carcinogen, 3'-methyl-4-dimethylaminoazobenzene (3'-MeDAB) for periods of 10–16 weeks. Most of the rats developed liver cancers between 13 and 26 weeks. The basal activity and responsiveness to isoproterenol, glucagon and fluoride of the adenylate cyclase in the 1100 g fraction of liver homogenates from these animals was compared to that of control animals throughout the period. By 2 weeks after starting the diet there was a 150–250% increase in isoproterenol responsiveness of the cyclase which reached a maximum of 500–900% by 6–9 weeks, depending on the ages of the animals. The isoproterenol responsiveness of the cyclase had the characteristics of a β-adrenergic response, and the vmax was increased in the test animals rather than a shift in the dose–response curve obtained. There was a significant progressive increase in basal enzyme activity over the experimental period. Fluoride responsiveness was unchanged, and the glucagon responsiveness of the enzyme was depressed throughout the entire period. With the development of tumours the isoproterenol response decreased, but did not fall below normal levels. Hormone responsiveness of established tumours was variable but never high.

It is concluded that the appearance of more effective β-adrenergic stimulation of adenylate cyclase may be related to neoplastic transformation, but not to the uncontrolled growth of established tumours.

3. OBSTRUCTIVE LIPOPROTEIN (LP-X) AND LIVER DISEASE

H. N. Magnani, P. Alaukovic and R. Poley

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(Introduced by D. Heath)

Obstructive liver disease is characterized in > 94% of cases by the presence of an abnormal lipoprotein designated LP-X. It is absent only in very early cases of cholestasis or in severe hepatic decompensation. In the same subjects the incidence of AP levels > 33 KA units was > 82%, LP-X is not found in non-cholestatic jaundice. Assay of its concentration is useful in two areas of hepatic disease diagnosis: (a) the differentiation of infants with neonatal hepatitis from those with biliary atresia, (b) differentiation of intra- from extrahepatic cholestasis in adults. In the former a 100% success rate has been achieved, but in the latter several disorders impair the ability of the LP-X alone to achieve this distinction. However, the combined use of the LP-X assay, routine LFTs and tests for the presence of antibodies to mitochondria and smooth muscle, greatly facilitate the differentiation and may in future be used to reduce the necessity for various intubation and cholangiographic procedures and the incidence of diagnostic laparotomies.

4. THE EXCRETION OF BILE PIGMENTS IN RATS AFTER INTRAVENOUS INJECTION OF BILIVERDIN ISOMERS

J. Barrowman, R. Bonnett and P. Bray

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In the metabolism of haem, the cleavage of the protoporphyrin ring occurs at the α-methylene bridge yielding biliverdin IXa; the reaction is catalysed by haem α-methyl transferase, and the β, γ and δ isomers do not appear to be formed in this process. Biliverdin IXa is subsequently reduced by biliverdin reductase to bilirubin which is taken up by the hepatocyte and conjugated with glucuronic acid by glucuronyl transferase prior to its excretion in bile.

The present study has examined in rats the excretion of bile pigments following the intravenous injection of all four isomers of biliverdin. Haem was bio-synthetically labelled using duck erythrocytes and 5-amino laevulinic acid-414C (Custer, Abei, Chipman & Iber, 1964, Journal of Laboratory and Clinical Medicine, 64, 820). Crystalline haemin was isolated and converted chemically to a crude mixture of 14C-labeled isomeric biliverdin dimethyl esters which were separated by thin layer chromatography (t.l.c.) (Bonnett & McDonagh, 1973, Journal of the Chemical Society, Perkin, 1, 881). The esters were subsequently hydrolysed with trifluoroacetic acid. Adult rats with polythene cannulae placed in the common bile duct at operation were given the individual labelled biliverdins by intravenous injection. Bile was collected for