Paediatric Research Society

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Abstracts of Papers

pH Changes in Children with Burns. F. Harris and J. Black. (*Department of Child Health, University of Sheffield*). As part of a study in depth of metabolic changes in burned children, serial acid-base studies were done. In order to evaluate the findings further, a group of children admitted for elective minor surgery had as part of the pre-operative assessment, an analysis of the acid-base status. A small number had serial post-operative analyses done. The results in patients with burns of varying severity were presented and compared with the data obtained from children undergoing minor elective surgery. The clinical significance of these findings was discussed.

Observations on Fat and Carbohydrate Metabolism in Generalized Lipodystrophy. M. Segall and J. Lloyd (*Institute of Child Health, London*). Investigations of fat and carbohydrate metabolism were made on a 10-month-old girl with generalized lipodystrophy; her parents were second cousins and her appearance was abnormal from birth. Subcutaneous tissue obtained by open biopsy showed no macroscopical fat; histologically a few isolated areas of adipose tissue were seen and the cells contained little lipid. Analysis of lipid extracted from the tissue showed a greatly reduced triglyceride content (0.4% wet weight), with a low percentage of linoleic acid (3.0% of total fatty acids).

Fasting plasma non-esterified fatty acid (NEFA) concentrations were normal (0.52–1.15 mEq/l.); the percentage of linoleic acid was reduced (2.3–4.6%). After subcutaneous adrenaline (0.01 mg./kg.) plasma NEFA concentrations showed only a transient increase. After oral glucose (2 g./kg.) the plasma glucose and insulin levels rose but the normal reduction in plasma NEFA did not occur; the glucose tolerance curve showed no diabetic features. Fasting plasma triglyceride concentrations were variable (82–648 mg./100 ml.) but were usually raised, and paper electrophoresis showed a prominent pre- β -lipoprotein fraction. Triglyceride fatty acids showed an increased percentage of palmitic acid (41.5–46.7%) and reduced percentages of oleic acid (35.1–41.3%) and linoleic acid (0.8–3.4%). After oral glucose there was an increase in plasma triglyceride from 84 mg./100 ml. to 146 mg./100 ml.; this is an abnormal response. An oral fat

load test (2.2 g./kg.) showed delayed clearing of plasma triglyceride, and the post-heparin lipolytic activity was very low (0.08 μ Eq fatty acid/ml. plasma per min.). Fasting plasma triglyceride and pre- β -lipoprotein were reduced by a low fat diet. These findings show that fasting plasma NEFA is maintained at normal concentrations despite the gross depletions of adipose tissue; however, the regulation of plasma NEFA by glucose and insulin appears abnormal. The hypertriglyceridaemia results mainly from a defect in peripheral triglyceride clearance.

Nephrotoxic Effect of Vitamin D Therapy in Vitamin D-Refractory Rickets. M. Moncrieff (*Introduced by R. H. R. White*). Published in full, in *Archives of Disease in Childhood* (1969), 44, 571.

Incorporation of Methionine Sulphur into Cysteine *In Vitro* by Fibroblasts Deficient in Cystathionine Synthetase. P. F. Benson, J. L. Hamerton, and V. Young (*Paediatric Research Unit, Guy's Hospital Medical School, London*). The main pathway for the incorporation of methionine sulphur into cysteine involves its transference to the carbon residue of serine. A step in the metabolic pathway involved is catalysed by the enzyme cystathionine synthetase.

Though the activity of cystathionine synthetase of cultured fibroblasts from patients with homocystinuria was considerably reduced (4 controls 1.7 to 2.3; 2 homocystinurics 0.2, 0.4 μ mole of cystathionine formed per hr. per g. protein), the rate of incorporation of 35 S-methionine into protein as 35 S-cysteine and 35 S-methionine was similar to both types of cells.

The utilization of an alternative transsulphydrase pathway by homocystinuric cells was investigated. In this pathway homocysteine desulphydrase catalyses the conversion of methionine sulphur into hydrogen sulphide. The latter then reacts with ammonia and pyruvic acid, catalysed probably by a reversal of the cysteine desulphydrase reaction. In cells from subjects with homocystinuria a raised activity was found of cysteine desulphydrase (4 controls 8.3 to 14.6 units; 2 homocystinurics 23.6, 48.3 units). Homocysteine desulphydrase activity was similar in controls and patients (4 controls 8.9 to 12.5 units; 2 homocystinurics 10.1, 11.1 units).

The characteristic biochemical abnormalities in

blood and urine from patients with homocystinuria indicate that the desulphydrase pathway is not sufficiently active to prevent homocysteine and methionine accumulation *in vivo*. Since the experiments on ^{35}S -methionine incorporation described above measured only incorporation of ^{35}S into protein, it is possible that cysteine synthesized by the desulphydrase pathway is incorporated into protein preferentially to pre-existing cysteine in metabolic pools. Alternatively, the low levels of cystathioninase activity in normal fibroblasts may constitute a block in conversion of methionine sulphur to cysteine sulphur in normal cells, even though cystathionine synthetase activity is adequate.

Application of Test of Adrenocortical Sensitivity to Bioassay of ACTH and to Assessment of Possible Altered Adrenocortical Sensitivity. M. Friedman (Clinical Research Centre, Northwick Park, and University College Hospital, London). The administration of pharmacological quantities of ACTH followed by the measurement of plasma or urinary steroid levels is the basis of all currently used tests of adrenal function. A test based on the administration of physiological amounts (nanogram quantities) of synthetic ACTH compounds has been devised to test adrenal sensitivity (Landon *et al.*, 1967). This procedure has proved to be valuable for assaying corticotrophin activity in man, and for assessing adrenocortical sensitivity in children receiving prolonged ACTH therapy.

A recently synthesized analogue of corticotrophin, the pentacosapeptide D-serine¹-norleucine⁴-valinamide²⁵-B¹⁻²⁵ corticotrophin (DW-75; Sandoz) was found to have an activity of 625 i.u./mg. when assayed by the rat adrenal ascorbic acid depletion test of Sayers. The assay value obtained by this compound using the Sayers test was five times that obtained for synthetic porcine corticotrophin and the tetracosapeptide synacthen (Ciba). D.W.-75 has been administered to human subjects in pharmacological and physiological concentrations and the adrenal response was measured. The results indicate that on a weight for weight basis, D.W.-75 has similar duration of action and adrenal stimulating properties to other synthetic polypeptides with adrenocorticotrophin action. These findings suggest that the assay values based on adrenal ascorbic acid depletion test obtained with polypeptides having corticotrophin-like activity bear little relation to the behaviour of these preparations when administered to man.

Adrenocortical sensitivity was assessed in a group of children who had been treated with ACTH for prolonged periods because of the possibility of altered adrenocortical responsiveness as a result of repeated stimulation. The results indicate neither increased nor decreased adrenocortical sensitivity as a result of prolonged adrenal stimulation with exogenous ACTH.

REFERENCE

- Landon, J., James, V. H. T., Wharton, M. J., and Friedman, M. (1967). Threshold adrenocortical sensitivity in man and its possible application to corticotrophin bioassay. *Lancet*, 2, 697.

Mechanism of Bronchial Constriction in Asthma. R. S. Jones (Institute of Child Health, Liverpool). The lability index was measured in 24 normal subjects aged 20-35 years and found to be between 4 and 21% with a mean of 12%. The lability index measures the tendency of the bronchi to dilate and constrict, using the FEV as an index of airway resistance. Figures less than 20% are regarded as normal. On another day each subject was given 100 mg. of propranolol by mouth, 40 minutes before a repeat measurement of lability. There was a significant increase in lability for the group as a whole (range 6-42%; mean 18%; $p < 0.01$). When the criteria for defining asthma in terms of lability were applied, 8 subjects had moved into the asthmatic range. The difference in lability for this group, with and without propranolol, was highly significant ($p < 0.01$). In the group formed by the remaining 16 subjects, there was no significant difference. The pattern of bronchoconstriction after exercise in the group of 8 was exactly similar to that found in asthma.

In the normal subject at rest, muscle cell receptor activity causing relaxation (R) must exceed receptor activity causing constriction (C), since the bronchioles are almost fully dilated and stable. No constriction occurs after β -blockade at rest, so R must still exceed C, despite the smaller value of R.

On exercise, when constriction occurs after blockade, C must exceed R. Hence, enhanced activity (C) of undefined receptors must occur on exercise. In the absence of blockade, this activity results in minimal or no bronchoconstriction because it is opposed by the intact adrenergic mechanism.

The fact that 40% of asthmatics develop constriction at rest after propranolol indicates that they are dependent upon β -receptor activity for the prevention of constriction to a degree which the normal subject is not dependent. β -receptor activity is probably enhanced in the asthmatic therefore, but it may not be sufficient to maintain full dilatation at rest. β -receptor activity in these is presumably opposed by constrictor receptors activated by histamine or 'H'-like substances.

Post-exercise bronchoconstriction in asthma may not be due to an abnormal mechanism during exercise, but to the normal constrictor mechanism on exercise operating on a bronchus which is less stable than normal due to histamine or 'H'-like substances.

The phenomenon of abnormal lability, which is the determinant of clinical asthma, may therefore depend upon two mechanisms: (1) constriction due to activation of receptors by substances released after an allergic reaction, and (2) an inherently less stable bronchial tree which renders the individual vulnerable should an allergic reaction occur.

Muramidase (Lysozyme) Excretion in Children. T. M. Barratt and R. Crawford (Department of Immunology, Institute of Child Health, London). (Introduced by J. Lloyd). Lysozyme is a low molecular weight protein (14,000) that is synthesized by granulocytes and liberated