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

into the extracellular fluid when they are destroyed. The principal site of catabolism of extracellular lysozyme is the kidney: it enters the glomerular filtrate, and is re-absorbed and catabolized by the proximal tubule.

The fractional excretion of lysozyme (clearance of lysozyme/clearance of creatinine, C_L/C_C) was measured in healthy adults:

$C_L/C_C = 1.05 \pm 0.96 \times 10^{-3}$ (mean $\pm$ SD, $n = 16$). C_L/C_C showed a positive correlation with the rate of urine flow, but no correlation with albumin excretion was observed.

In healthy full-term newborns, C_L/C_C was not significantly increased:

$C_L/C_C = 1.44 \pm 1.02 \times 10^{-3}$ ($n = 8$).

This aspect of proximal tubular function is therefore normal in the neonate.

C_L/C_C was normal in the nephrotic syndrome in children:

$C_L/C_C = 0.76 \pm 0.68 \times 10^{-3}$ ($n = 12$).

These data indicate that the presence of high concentration of albumin in proximal tubular fluid does not interfere with lysozyme reabsorption, and support the hypothesis that small and large proteins do not compete for the same transport system.

In 4 children with the Fanconi syndrome due to cystinosis, the excretion of lysozyme was much increased, confirming proximal tubular dysfunction:

$C_L/C_C = 56 \pm 10^{-3}$ (mean; range = $20-84 \times 10^{-3}$)

The possibility of local production of lysozyme was examined in children with pyuria. In such children with structurally normal kidneys and normal blood ureas the urine lysozyme/creatinine concentration ratio did not differ from that of the normal adults.

The excretion of lysozyme therefore offers a simple test of proximal tubular function, and, in contrast to techniques of assessment of amino acid excretion, provides easily obtained quantitative data to which statistical techniques can be applied to assess the natural history and response to therapy of tubular disorders.

Use of Rat Fetus in Experimental Teratology.

C. L. Berry (*Institute of Child Health, Guilford Street W.C.1*). Abnormalities of cell growth, differentiation, or morphogenetic movements during organogenesis represent the principal cause of major malformations in man. In teratological experiments it is difficult to observe organogenesis directly in mammals. The rat fetus may be grown in organ culture throughout the period of organogenesis, and this experimental model is of considerable value. It enables the possible effects of maternal metabolism on teratogens to be excluded, and the ability to initiate the direct absorption of antibody without the possibility of maternal cross-reaction is useful. The relations of growth and differentiation in this system, and the effects of trypan blue, methotrexate, and specific antisera have been studied.

Porosity of Placenta in Mouse to Maternal Cells. R. D. Barnes (*Department of Haematology, Institute of Child Health, London*). There have been

occasional reports of maternal cells in the cord blood of newborn infants; however, it is commonly accepted that this is perhaps an infrequent occurrence. In theories concerning the immunological significance of the foeto-maternal barrier the placenta has been considered to protect the fetus (an allograft) against maternal rejection.

Using an ovum transplantation model it has now been shown that a substantial number of nucleated cells from the mother are present in the young mice. Fertilized ova from normal CFW mice have now been successfully uterine-nurtured to term in the uterus of pregnant CBA/T6T6 mice, having cells with a characteristic chromosomal marker. Surprisingly, CFW mice derived in this way have up to 30% of maternal cells with the chromosomal marker—in fact these animals are chimeras. In these animals there is no evidence for the rejection of this 'graft' and no apparent evidence of any graft-versus-host reaction. The morphological nature of these foreign maternally derived cells is as yet unknown, but it seems likely that they represent nucleated blood cells. If these cells include maternal lymphocytes then their apparent immunological inactivity as a graft towards a genetically foreign host needs explanation. Chimerism here has been demonstrated in uterine-nurtured animals, and conceivably the surgical procedure of ovum transplantation itself might be held responsible. Preliminary data, however, suggest that chimerism in mice is a natural phenomenon since normally derived mice have maternal cells.

The significance of these observations might well influence theories of genetic transmission and development of immune tolerance. In addition, maternally derived cells may play a part in the development of both autoimmune disease and neoplasm, and these cells could conceivably be utilized in an active immunotherapy programme of neoplasms.

Blood Viscosity in Newborn Infant and Diagnosis and Treatment of Hyperviscous States. T. Mackintosh (*Royal Infirmary, Dundee*). Viscosity is the factor that determines how a fluid will behave when it flows. The viscosity of blood is not fixed but varies with the rate of shear, gradually increasing as shear rate decreases.

The normal range of blood viscosity was determined by studying 110 full-term, singleton, normal infants weighing over 2600 g., using a Wells-Brookfield synchroelectric microviscometer model L.V.T. (shear rate range 1.16 to 232 sec^{-1}), with a special attachment for small blood samples. This confirmed that blood was a non-Newtonian fluid, with a viscosity varying from 5.47 c.p.s. at a shear rate of 232 sec^{-1} to 33.6 c.p.s. at 1.16 sec^{-1} . A close correlation exists between blood viscosity and the venous PCV, but there is no relation to birthweight or time from birth.

Further studies showed that respiratory distress (20 infants) and prematurity (21) were not usually associated with increased viscosity, but the mean for 12 dysmature infants is only just within the normal range.

16 infants had signs attributable wholly or in part to