vaccines, but it raises special problems because of the potential risk of transmitting the infection to pregnant women.

This risk, together with the need to select a cell substrate other than monkey kidney tissue for vaccine production, led to intensive research for alternative methods. Progress has been rapid,[21-23] and three vaccines have been produced, giving similar results in susceptible children. A seroconversion rate of close on 100% has been achieved, and antibody is well maintained for at least three years. Clinical reactions in children are mild, but excretion of virus to a greater or less degree occurs with all vaccines. Attempts to reduce the amount of virus excretion by further attenuation resulted in considerable loss of immunizing capacity.[24 25] Comparative trials with these three vaccines carried out in Great Britain by J. A. Dudgeon and colleagues[26] showed that there was a higher reaction rate, though reactions were mild, in adults than children, and that joint pains were more frequent in adult females than in males or in children. This finding is in agreement with other observers.[21-23]

A report in this week's issue of the *B.M.J.* at page 531 by Dr. I. B. Hillary and colleagues tells of a clinical trial with a vaccine in children in Ireland. Though excretion of virus by vaccinated persons is common, this and the other studies do not show any evidence of transmission of the disease. This is due in part to the fact that the amount of virus in the throat after vaccination is very small compared with either a natural or a congenital infection and also to the fact that the virus is attenuated. Nevertheless, the fact that virus reaches the throat means that viraemia has occurred. It may be limited, and it probably is; but vaccine virus strains have been recovered from the blood of vaccinated persons and also from the placenta after therapeutic abortion. Though there is no evidence of foetal infection with attenuated rubella strains there is equally no evidence that an attenuated strain is non-pathogenic for the foetus. It follows therefore that live rubella vaccines should not be administered to women who are pregnant at any stage of their pregnancy or to those who might be pregnant.

The prelicensing statement issued by the U.S. Public Health Service Advisory Committee on Immunization Practices[20] sets out recommendations for rubella virus vaccines. It is recommended that in the U.S.A. vaccine should be given to girls and boys between 1 year of age and puberty, with an initial priority for children in kindergarten and elementary school. This should reduce the spread of infection in this highly susceptible group, but until more is known about the persistence of immunity (only three years have elapsed since the original trials) it would be premature to carry out mass vaccination of this age group with the idea of eradicating rubella. This may be achieved in time but is not a necessary first step, certainly so far as Britain is concerned. It may be considered advisable to defer immunization until later in childhood and before puberty in the hope that immunity will last throughout the child-bearing years. These are some of the problems now being considered. Their solution may lead in the foreseeable future to a reduction in the incidence of congenital rubella defects.

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[22] International Conference on Rubella Immunization, Bethesda, Maryland, 1969, *American Journal of Diseases of Children*, 1969, in press.

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Research into Calcium Metabolism

Stone disease of the urinary tract is thought to affect about 3% of the population and to be responsible for 260,000 lost working days every year in Britain. Moreover, the incidence seems to be rising in the western world—in part possibly owing to changes in diet and a more sedentary life. A survey in Norway showed that in 1959 there were more operations for urinary stone than for appendicitis. These points were emphasized at an open-day for the press held by the Medical Research Council's Mineral Metabolism Unit on 22 May. The Unit is housed in the General Infirmary at Leeds, and was formed five years ago as the successor to the Council's Metabolic Disturbances in Surgery Unit there. Its director is now Dr. B. E. C. Nordin. A feature of the unit is that it contains an unusually large number of experts in the fields of basic sciences. Of the complement of 45 scientists, only five are medical men.

At present the unit's two main interests are research into urinary stone disease and osteoporosis. Since calcium-balance studies there have shown that, compared with normal people, stone-formers have an increased intestinal absorption and an increased urinary excretion of calcium, the unit has devised a working hypothesis of the formation of stones in the urinary tract. Most urinary tract calculi, it is suggested, result from excessive excretion of calcium or oxalic acid or both. This leads to increased urinary supersaturation, and subsequently crystal nucleation and crystal aggregation within the renal tubules. Eventually a calcium oxalate " microlith " is formed, which migrates to the renal calyx or ureter, where it grows to form true stones. Some of the earlier stages of this hypothesis have been shown to be valid, and the unit is now investigating a scheme for prophylaxis of calculi in stone-formers. These measures might include a high fluid-intake, a low calcium and oxalate diet, and the administration of magnesium salts; another possibility, which is at present being tested in animals, is the use of non-toxic substances to inhibit the formation of crystals in the urine.

Work on the other main interest—osteoporosis—has concentrated so far on developing a method of assessing this objectively, to replace the previous unsatisfactory subjective visual assessment of an *x*-ray film. Two quantitative measures have been developed. The first method is *x*-ray densitometry, in which *x*-ray films of a patient's bones are compared with those of a standard bone or aluminium strip incorporated on the same film, using a scanning device. The second is isotope densitometry, in which the patient's arm is scanned in a machine using a source of gamma rays. This measures the density of parts of three standard bones (the lower end of the radius and ulna, and the middle of the second metacarpal). From these measurements it has been found possible to predict the total skeletal weight of an individual subject.

One explanation of the frequency of osteoporosis after the menopause may come from the unit's study of bone metabolism in tissue culture. This technique, which uses calvaria taken from mice, has shown that parathyroid hor-

mones can break down bone more easily when oestrogens are not present. Hence after the menopause the action of parathyroid hormone on the bone is unopposed, and this may eventually result in osteoporosis.

Clearly since it was formed five years ago the Mineral Metabolism Unit at Leeds has made great progress in two fields responsible for much human suffering. Further achievements from this unit seem assured.

Nephrotic Syndrome in Adults

"Nephrosis" once passed for a diagnosis, but the "nephrotic syndrome" is now synonymous with heavy proteinuria plus its non-specific consequences—hypoalbuminaemia and oedema, alpha-2 hyperglobulinaemia, hyperlipaemia, and lipiduria. Its causes are legion.[1] About 25% of adults with the syndrome have systemic diseases, back pressure on the kidney, or drug allergy as the primary cause.[2]

In a study reported at page 533 of this issue of the *B.M.J.* Drs. P. Sharpstone, C. S. Ogg, and J. S. Cameron excluded patients with recognized causes, but renal biopsy none the less showed amyloidosis in 6 out of 56 patients. Several other studies of adult nephrotic syndrome have uncovered a comparable group of patients with unexplained renal amyloid[3 4] who progress rapidly to renal failure and are not helped by steroid therapy. The remaining 50 patients were assigned by Sharpstone and his colleagues to the three conventional histological categories—minimal change, and membranous and proliferative glomerulonephritis.[5] Since this classification is the basis of treatment in the adult it deserves closer scrutiny. The first two categories are near to being distinct diseases, though their aetiology remains obscure. Proliferative glomerulonephritis on the other hand is a collection of widely differing clinical and pathological patterns.

Minimal change[6 7] is defined as the absence of abnormality in the glomeruli on light microscopy and the fusion of epithelial foot processes over normal basement membrane on electron microscopy. The corresponding clinical syndrome comprises heavy, selective proteinuria (usually over 8 g. per day at the height of the illness), slight or absent microscopical haematuria, normal blood pressure, and normal excretory function except in the presence of hypovolaemia.[8] The onset is often explosive, but spontaneous remission is common within two years.[9] Corticosteroids produce prompt clinical remission in about 80% of patients[6] and restore the ultrastructure to normal.[10 11] Six of the eight patients studied by Sharpstone and his colleagues lost their proteinuria within eight weeks. Most of the reported failures on steroid therapy have been diagnosed by light microscopy, and they no doubt include some cases of unrecognized focal glomerulonephritis. Relapse after withdrawal of steroids is a major problem in children and occurred in three of the adults in this series. Cyclophosphamide[12] produces a remission that persists after withdrawal of therapy in children who are otherwise dependent on steroids, and it deserves trial in the same circumstances in adults.

Membranous glomerulonephritis ("extramembranous glomerulonephropathy" to the purists) is shown by electron microscopy to result from the deposition of foreign material on the epithelial side of the basement membrane. These deposits are shown as spiky projections on silver stains, and fluorescent microscopy shows the presence in them of gamma-globulin and the C'3 component of complement. One or other of these special techniques is required to establish the diagnosis, since thickening of the basement membrane is seen in sections stained with haematoxylin and eosin in other conditions. It is associated with moderate to heavy unselective proteinuria (often present for years before the onset of nephrotic syndrome), considerable microscopical haematuria, late onset of hypertension, and slow, relentless progression to renal failure. Spontaneous remission is rare,[13 14] and corticosteroids are almost universally ineffective. The few reported steroid-induced remissions have not been accompanied by reversal of the histological lesion.[14 15] The role of immunosuppressive drugs has not been fully assessed, but preliminary results are not too encouraging.[16 17]

Proliferative glomerulonephritis can be divided into seven or eight subgroups.[7] Sharpstone and colleagues used five subdivisions, including a large heterogeneous group of "all other proliferative." Their first category corresponds to acute nephritis following streptococcal or other[18] infections. The other four categories are of unknown aetiology. The depression of renal function, its rate of progression, and the tendency to spontaneous remission vary widely except in the category "with extensive crescents," which has a uniformly bad prognosis. The selectivity of protein clearances varies and is no guide to the effect of steroid therapy in the adult.[6] Indeed a Medical Research Council trial showed a significant mortality risk from steroid therapy in adult patients with nephrotic syndrome and no significant benefit in those with proliferative glomerulonephritis.[9] Sharpstone and colleagues report in a second paper at page 535 on a comparison between steroid therapy (prednisolone) and a combination of azathioprine and low-dose steroids. Though there was some improvement in creatinine clearance and reduction of proteinuria, the two regimens were not significantly different in their results. Azathioprine is also the object of a multicentre trial

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