ample scope for the surgical relief of disability in these patients with "fibrous dysplasia".

[1] Hunter, D., and Turnbull, H. M., *British Journal of Surgery*, 1931, **19**, 203.
[2] Lichtenstein, L., *Archives of Surgery*, 1938, **36**, 874.
[3] Albright, F., Butler, A. M., Hampton, A. O., and Smith, P., *New England Journal of Medicine*, 1937, **216**, 727.
[4] Falconer, M. A., and Cope, C. L., *Quarterly Journal of Medicine*, 1942, **11**, 121.
[5] Gibson, M. J., and Middlemiss, J. H., *British Journal of Radiology*, 1971, **44**, 1.
[6] Dockerty, M. B., Ghormley, R. K., Kennedy, R. L. J., and Pugh, D. G., *Archives of Internal Medicine*, 1945, 75, 357.
[7] Henry, A. N., M.Ch. Thesis, University of Dublin, 1963, 87.
[8] Harris, W. H., Dudley, H. R., and Barry, R. J., *Journal of Bone and Joint Surgery*, 1962, **44-A**, 207.
[9] Henry, A., *Journal of Bone and Joint Surgery*, 1969, **51-B**, 300.

The Pill and Folate Metabolism

It looks as though an action on folate metabolism must now be added to the long list of effects of oral contraceptives. While they are certainly no cause for alarm, the observations raise interesting questions about the way in which dietary folate is utilized. A. M. Shojania and his colleagues[1 2] found that women taking oral contraceptives had a lower average concentration of folate in the serum and red cells and a higher figlu excretion in the urine than control persons. These early observations were not confirmed by others,[3 4] and it seems likely that the majority of women on the pill can absorb sufficient folate from their food to avoid becoming deficient. Nevertheless there have been a handful of reports of megaloblastic anaemia.[5 6] Of the seven patients described by R. R. Streiff[5] five responded satisfactorily to daily doses of 250 µg folic acid while still taking oral contraceptives and two had a reticulocyte response when the contraceptives were discontinued. When absorption tests were carried out in women on the pill[5 7] it was found that folic acid (monoglutamate) was utilized normally, while serum folate levels fell by as much as 50% after ingestion of folic polyglutamates, the form in which dietary folate is present.

Folic polyglutamates in the diet are broken down by a conjugase enzyme in the small intestine to the monoglutamate (folic acid), which is then absorbed, though it is uncertain whether this action occurs in the lumen of the gut or in the mucosa. The anticonvulsant, phenytoin, appears to inhibit conjugase activity in vitro,[8 9] but few epileptic patients taking the drug develop megaloblastic anaemia or even folate deficiency, and individuals must vary considerably in their sensitivity and ability to utilize dietary folate. The similarity between this situation and that of women on the pill or during pregnancy is striking, but it has not yet been established whether conjugase inhibition occurs in these latter two circumstances. It would be tempting also to assume that the tendency to folate deficiency in pregnancy is related to the inhibition of folic polyglutamate absorption that occurs in women on the pill, but a recent study[10] showed no difference in absorption of mono- and polyglutamates by women in the latter half of pregnancy. More work on these lines is needed together with tests of conjugase activity similar to those involving phenytoin, not only to see if there is conjugase inhibition but also to determine which of the steroid hormones or their metabolites inhibit the absorption of polyglutamates. Such observations may eventually solve the riddle of folate deficiency in pregnancy.

In the meantime it must be stressed that oral contraceptives are an unusual cause of megaloblastic anaemia and that malnutrition, malabsorption, liver damage, and perhaps pregnancy itself are more likely. Even in women taking oral contraceptives these causes should be excluded. Provided this is done, an adequate dietary intake plus 250 µg folic acid daily should be sufficient to maintain the health of the few susceptible individuals who wish to continue taking the pill.

[1] Shojania, A. M., Hornady, G., and Barnes, P. H., *Lancet*, 1968, **1**, 1376.
[2] Shojania, A. M., Hornady, G., and Barnes, P. H., *Lancet*, 1969, **1**, 886.
[3] Spray, G. H., *Lancet*, 1968, **2**, 110.
[4] McLean, F. W., Heine, M. W., Held, B., and Streiff, R. R., *American Journal of Obstetrics and Gynecology*, 1969, **104**, 745.
[5] Streiff, R. R., *Journal of the American Medical Association*, 1970, **214**, 105.
[6] Paton, A., *Lancet*, 1969, **1**, 418.
[7] Necheles, T. F., and Snyder, L. M., *New England Journal of Medicine*, 1970, **282**, 858.
[8] Hoffbrand, A. V., and Necheles, T. F., *Lancet*, 1968, **2**, 528.
[9] Rosenberg, I. H., Godwin, H. A., Streiff, R. R., and Castle, W. B., *Lancet*, 1968, **2**, 530.
[10] McLean, F. W., Heine, M. W., Held, B., and Streiff, R. R., *Blood*, 1970, **36**, 628.

Polio Risks

The routine use of live oral poliovirus vaccine on a mass scale began in a number of countries in the spring of 1960. It followed three years of thorough international collaborative studies. These had proceeded step by step from an initial clinical trial in a few volunteers to extensive field evaluation on millions of people. The studies showed that the Sabin strains of attenuated virus provided a high level of protection without producing harmful effects and that, though the virus could spread from vaccinated persons to household contacts, the transmitted infection also was harmless but immunizing. Since 1960 more than two thousand million people have received the vaccine, but even to-day vaccination presents problems, some of which are only just emerging. Paradoxically, the two main ones are the poor performance of the vaccine in tropical countries and the repercussions of its sheer efficacy in the temperate zone.

In tropical countries a high proportion of infants and young children are subject to a seemingly endless succession of intestinal infections, which can prevent the live vaccine from establishing itself in the intestines, a prerequisite to the development of immunity. In view of this and the difficulties in carrying out mass vaccination programmes it is not surprising that most tropical countries reported a few hundred new cases of paralytic poliomyelitis during 1969, whereas very few in the temperate zone had as many as 15 cases.[1]

In temperate countries mass vaccination programmes sustained over a period of a few years have rendered paralytic poliomyelitis a rare disease. The public feel increasingly secure from the disease and consequently are losing interest in vaccination. The introduction of new immunization schedules in Britain failed to halt the decline in infant vaccination rates, and it seems that further exhortation of defaulting mothers will have little effect on this trend. Few parents withhold their consent to the vaccination of school children, and the offer of vaccine to school entrants, as recommended in this country,

should ensure that the immunity of older children is maintained.

It is conceivable that in future those responsible for mass immunization programmes may have to combat not only indifference to vaccination but also active opposition arising from the fact that the vaccine carries a remote risk of causing paralytic poliomyelitis. The risk was found to be less than one case per million doses of vaccine used in the U.S.A. during 1961-3[2] and 1964-8,[3] whereas in England and Wales it was one case per four million doses of vaccine used during 1962-4[4] and 1965-8.[5] Vaccine-associated paralytic poliomyelitis is not necessarily restricted to recipients of vaccine but may involve close contacts.[3 5] Nevertheless, if the vaccination programme were to be fully carried out in this country, it is highly unlikely that there would be more than four vaccine-associated cases of paralytic poliomyelitis per year. Since completion of a mass vaccination programme almost completely suppresses paralytic poliomyelitis due to wild virus but at the same time may cause paralytic poliomyelitis on rare occasions, there could in future be more new paralytic cases attributable to the vaccine virus than to wild virus. If vaccination were neglected, however, outbreaks of poliomyelitis, such as that in Blackburn during 1965,[6] are likely, particularly since there is a constant and substantial risk of the virus being imported. There were 707 new cases of paralytic poliomyelitis and 59 deaths in England and Wales in 1961, the last year before live vaccine was used here on a large scale. All were due to wild virus. In 1969 there were only 9 cases, and there have been no deaths since 1966.[7] The choice is clear: a fully carried out vaccination programme, which carries a remote risk of paralytic poliomyelitis, or a neglected programme, which could allow the wild virus to cause new outbreaks. The biggest problem confronting us to-day is one of public apathy. It erodes vaccination programmes.

1 *World Health Statistics Report*, 1970, **23**, No. 8.
2 Henderson, D. A., Witte, J. J., Morris, L., and Langmuir, A. D., *Journal of the American Medical Association*, 1964, **190**, 41.
3 Hopkins, C. C., Dismukes, W. E., Glick, T. H., and Warren, R. J., *Journal of the American Medical Association*, 1969, **210**, 694.
4 Miller, D. L., and Galbraith, N. S., *British Medical Journal*, 1965, **2**, 504.
5 Miller, D. L., Reid, D., and Diamond, J. R., *Public Health (London)*, 1970, **84**, 265.
6 Moss, P. D., Durge, N. D., Robertson, L., and Cowburn, G. R., *Lancet*, 1968, **2**, 555.
7 *Annual Report of the Chief Medical Officer of the Department of Health and Social Security for the Year 1969*. London, H.M.S.O., 1970.

Cytomegalovirus Infection

Infection is not the same thing as disease. If an organism invades the body and multiplies in it, that is infection, but it may be silent and cause no reaction in the body other than a rise in antibody. In disease, on the other hand, the invading organism causes damage to tissues. This may be so slight that the patient has no symptoms and the damage can be detected only by laboratory tests. Many organisms can affect the human body in this way—in inapparent rubella, for example, subclinical poliomyelitis, or toxoplasmosis. Cytomegalovirus is another organism whose passage through the body is most often silent, though it can produce manifest disease.

In Sweden it has been estimated that over 90% of people aged 65 have been infected with cytomegalovirus,[1] yet illness due to cytomegalovirus infection has rarely been diagnosed in that country.[2] Part of the failure to detect cytomegalovirus disease is due to failure to look for it, but even when it is carefully sought few cases of symptomatic infection are found. G. Sterner and his colleagues[3] found only 17 cases in three years in Stockholm, though in one of the years 300 patients were studied with cytomegalovirus infection in mind. In their search they concentrated on patients with fever and atypical lymphocytes, patients thought to have septicaemia, and patients transferred from surgical wards because of unexplained fever. Paired sera were examined for complement-fixing antibodies, and urine for the presence of cytomegalovirus. The commonest symptom in the 17 patients was continued fever; the commonest findings were abnormal liver-function tests in all and atypical lymphocytes in the blood films of more than half. Sixteen of the 17 patients appeared well in spite of their fever.

Cytomegalovirus is like rubella virus in that, while it causes little damage to mature host cells, it destroys or severely damages fetal cells. Intrauterine cytomegalovirus infection tends, therefore, to cause severe congenital disease. The baby is born prematurely and obviously diseased. He is jaundiced and lethargic and his breathing is distressed. Often he has a purpuric rash, his liver and spleen are enlarged, he is anaemic and may have convulsions. Most of these infants die within a few days of birth, but a few recover, probably those few in whom the lungs and the brain have not been affected.[4] Some infected babies are born apparently normal but later show signs of severe brain damage, such as microcephaly, spastic diplegia, epilepsy, or blindness. These are all effects of the wide dissemination of the virus in developing fetal tissue. When an infant is infected after birth, the infection, by contrast, is usually silent. In necropsies of infants dying from other causes cytomegalovirus may be isolated from the salivary glands and the urine in as many as 10% with no evidence at all of any pathological changes due to the virus. In older children infection is common, especially in institutions, where in some instances half the children may be infected, excreting the virus in their urine or saliva for months or years,[5] yet showing no evidence of disease except, in a few, some enlargement of the liver. Very seldom does the infection break through to the clinical level as a rare cause of jaundice or of a prolonged fever in a child.

Symptomatic infections are seen more often in adults, and fever is the commonest symptom. The temperature is high and spiky and may continue for several weeks, yet the patient complains of little discomfort other than passing aches and pains. Serum bilirubin is normal, or only slightly raised, but there is usually a slight rise in some of the other tests of liver function, especially in transaminase levels. The white cell count may vary from 2,000 to over 20,000/mm^3, and atypical lymphocytes are often present. The blood picture and the liver-function tests may suggest infectious mononucleosis, and sometimes patients with cytomegalovirus disease have transient enlargement of lymph nodes, but in them the Paul-Bunnell test is always negative, as are immunofluorescent and complement-fixation tests for rising antibody titres against Epstein-Barr (EB) virus. Toxoplasmosis is another disease which presents with continued fever, lymphadenopathy, atypical lymphocytes, and negative Paul-Bunnell test, but the dye test and complement-fixation tests are strongly positive. If cytomegalovirus infection is suspected the urine should be examined for giant cells and cultured in human diploid cells for virus. Blood and other body fluid or tissue may also be cultured, and paired sera examined for rising antibody titre. If virus is isolated, and there is a rising serum antibody titre, this suggests that cytomegalovirus is the cause of the illness. If giant cells are also detected, this is further evidence of active cytomegalovirus disease.