15 and 16 with hypercortisonism secondary to immunosuppressive therapy in renal homotransplantation. Finding little evidence of bone necrosis, the authors prefer the title "arthropathy induced by steroid therapy." Although vascular lesions may be responsible for these changes, Velayos and his colleagues found little evidence of this in their material.

It is clear that destructive changes of bone occur in rheumatoid arthritis and systemic lupus erythematosus as well as in other disorders. R. D. Gerle[12] and his colleagues, for instance, report aseptic necrosis in femoral and humeral heads in association with chronic alcoholic pancreatitis. It is equally clear that similar changes have been reported in association with prolonged corticosteroid therapy in a number of unrelated conditions, ranging from eczema to tuberculous pericarditis[13] and thrombocytopenic purpura,[14] where the disease itself would seem unlikely to cause this complication. If Sutton and colleagues[9] are right, as they may well be, in regarding it as a rare but important complication of such therapy, careful watch for it in conditions other than rheumatoid arthritis, such as asthma, should be maintained in the future.

Time for Reappraisal?

The salient points in the latest report of the Regional Director for Europe of the World Health Organization[1] for the period July 1965–June 1966 are the efforts to improve health services in the regions round the Mediterranean basin (including north Africa), the increased scope of all types of educational programmes, and the attempts to gather ever more statistical data.

Malaria eradication has been completed in Yugoslavia, elimination of the last active foci in Greece is expected this year, and in Turkey the programme has advanced to the stage of being transferred to the local public health authorities. In Morocco the first stage of the programme has been started, but in Algeria it is not expected to get under way until 1968. A beginning has been made with an integrated programme for the control of communicable diseases of the eye in the north African countries, but organization of the new services is slow because of the difficulty in obtaining trained staff. Nutrition, maternity and child welfare, and immunization are all matters in which these countries are being helped.

The educational and training programmes initiated by the Regional Office deserve praise. To select only a few examples of the many projects in progress, the opening of the International Nursing School in Lyons in October 1965 means that there is now an institution parallel to the International Nursing School in Edinburgh opened two years ago. In both these schools courses and fellowships enable nurses from countries in the region to study basic and advanced techniques, and the education is designed to place increasing emphasis on social skills and preventive measures. Over a thousand medical and paramedical study fellowships were granted during the year, half being given to persons within the region and half to those coming to Europe. Thus the Regional Office is directly responsible for training people who will go from Europe and put their skill to use elsewhere, and at the same time it equips those coming from other continents to serve their own communities on their return. In short, the academic possibilities of Europe are exploited in twofold fashion for the benefit of the rest of the world. While most of these fellowships relate to public health and allied subjects, 5% have been awarded in the basic medical sciences this year.

As W.H.O. is primarily interested in public health, it is necessarily concerned with statistics. In his introduction to the report, the Regional Director emphasizes the importance of information about health and disease, and comments that the development of satisfactory statistical studies has lagged far behind improvements in the health services themselves. This may be true, but the information that can be extracted from statistical data is limited. Comparisons of mortality and morbidity rates between different countries, for instance, may be of little use because of differences in social habits and economic pressures in the countries concerned.

The statistical survey is the principal method by which the disease entities of major interest to Western Europe—are being tackled, though efforts are being made to enter wider fields of research. Large-scale controlled trials in rheumatoid arthritis, cancer, and ischaemic heart disease—certain countries are proposed to study the effect of reducing hyperlipidaemia in ischaemic heart disease, though much work has already been done on this subject on both sides of the Atlantic. The question arises, not for the first time, whether W.H.O. is wise to engage in projects outside its recognized fields of education and public health, and the onus of providing the answer lies with the Organization.

The countries of this region contribute together nearly half the budget of the W.H.O. (Britain contributes nearly 7%), though their total allocation from the headquarters budget is only about 12%. What then do we expect W.H.O. to do in Europe? After 20 years' service in this relatively well-developed region some reappraisal of the functions of the Organization is called for. Each country has its own health services, and most countries have a good enough economy to support a health programme. But W.H.O. bridges national frontiers and so is well placed to assist in the control of communicable diseases and facilitate the exchange of medical information. Perhaps the most constructive role for its European Regional Office would be to serve as an intelligence centre, helping individual countries to make the most of available knowledge and skill.

Mechanism of Aplastic Anaemia

Some drugs and other chemical substances cause aplastic anaemia, but the mechanism joining cause and effect doubtless varies. Sometimes depression of the bone-marrow is dose-dependent and predictable, as for example with busulphan, urethane, or nitrogen-mustard compounds. When drugs of this kind are stopped the blood cells and platelets usually return rapidly to normal levels. Other compounds only occasionally cause aplasia, at least in the usual therapeutic dose. For example, it has been estimated that one in 60,000 patients risks developing aplastic anaemia from chloramphenicol,[1] but there is no way of recognizing which will react unfavourably to the drug. Moreover, in only about one-quarter of patients with aplastic anaemia is it possible to attribute the condition to a drug or other chemical sub-

[1] Report of the Regional Director, World Health Organization Regional Office for Europe, Copenhagen. July 1965–June 1966.

stance, such as chloramphenicol, phenylbutazone, gold salts, streptomycin, and benzol derivatives. Nor is it possible to say what other of the physical and chemical factors prevalent today may be potential causes of aplasia—for example, *x* rays and petrol fumes. With this second class of compounds the course and ultimate prognosis is the same, whether the aplasia is drug-induced or not, and when a drug is known to be the cause the withdrawal of that drug does not appear to hasten recovery. Patients who survive may have a low platelet count for months or even years.[2]

The effect of chloramphenicol and similar compounds on biological material has been the subject of much study.[3-5] In micro-organisms and animal-tissue homogenates a small amount of chloramphenicol inhibits synthesis of protein, deoxyribonucleic acid (D.N.A.), and ribonucleic acid (R.N.A.). In normal bone-marrow a similar inhibitory effect is demonstrable *in vitro*, but only with high concentrations of the drug.[6] In patients a dose by mouth of 4 g. results in a blood level of 40–60 μg. per ml., a level well below what is apparently necessary for inhibition. One possible explanation is that a patient may have a biochemical defect of marrow cells, perhaps genetically determined, and this may lead to metabolic effects at a drug concentration which is relatively harmless to normal cells.[7] Alternatively, the sensitive patient may be unable to excrete the drug normally, so that a higher blood level is attained for a given dose. P. R. McCurdy[8] has shown that in patients with liver disease chloramphenicol is less readily conjugated, so that six to eight hours after administration concentration of the drug in the plasma is higher than in normal patients. A search for an excretion defect in sensitive subjects has proved fruitless,[9] and the problem of detoxification mechanisms in relation to marrow-depressant drugs requires further study.

Another interesting association is that between viral hepatitis and aplastic anaemia. R. N. Levy and co-workers[10] have reported it in five patients of their own and refer to four similar cases recorded by others. In only one case was there a history of drugs (several doses of a sulphonamide had been given at the onset of the illness). The aplastic anaemia occurred one to seven weeks after onset of hepatitis, at a time when the severity of the hepatitis was decreasing. Virus infections are a well-known cause of leucopenia. Pancytopenia is not common, but its occurrence, with temporary hypoplasia of bone-marrow, has been noted in association with rubella and the myxoviruses of influenza, parainfluenza, and mumps, while transient bone-marrow depression has also been reported in a case of virus hepatitis.[11]

Although viruses, particularly those containing R.N.A., appear to be a potential cause of marrow damage, severe aplastic anaemia is only rarely encountered in patients with virus infections who have received no antibiotic therapy. In Levy's series the concomitant liver insufficiency may have been relevant, especially if it is thought that failure of some detoxification mechanism is of importance in the pathogenesis of aplastic anaemia. Alternatively, virus-induced aplastic anaemia may be caused by individual susceptibility to a virus which is not ordinarily toxic to the marrow; or the virus infection may render the subject susceptible to some other potentially toxic factor. It has also been suggested that the bone-marrow failure may be explained on the basis of an autoimmune mechanism after the virus infection.[11]

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Unusual Twins

The evidence grows that medical studies of twins are not so reliable as has been thought.[1] One reason is that there is a multiplicity of types of twins. A third variety of twin intermediate between the monozygotic and dizygotic may occur. It is due to two sperms fertilizing one egg, and this might result either in two individuals or in a mosaic. S. M. Gartler and colleagues[2] have described an XX/XY mosaic female hermaphrodite who was almost certainly produced in this way. In other words she was a person who had some cells with a male and some with a female complement of chromosomes. All the tissues investigated were mosaic with mixtures of male and female cells, and it was possible to show that she had inherited both her father's genes (instead of only one of them) on the MNS blood-group system, both his Rh complexes, and both his genes controlling eye colour

An even more remarkable aberration is when monozygotic twins are not of the same apparent sex. The explanation of this may be that after the formation of a normal zygote there is non-disjunction of the sex chromosomes at the second cleavage division. In the first case described in France[3-5] one of the twins had both an X and a Y and the other only a single X chromosome. More recently[6] a similar pair has been reported in England. In both sets of twins there is no doubt about the monozygosity as judged by blood groups and serum proteins, hand and foot prints, and electrocardiographs. The clinical details of the English twins are of considerable interest. The female presented as a case of Turner's syndrome but was found to be an XO/XY mosaic. The male appeared entirely normal, though in all the cells studied he was found to be XO—that is, lacking the Y chromosome. However, because of his obvious masculinity it is postulated that he must possess a Y chromosome in some key organs such as the endocrine cells of the testis and that the XO cells elsewhere are fully competent to respond to the male-determining hormones. The authors consider that in the normal XY zygote, before twinning occurred, there was a loss in one of the early cell divisions of a Y chromosome, the zygote thus becoming a mosaic, XO/XY, and after twinning these cell lines persisted in both individuals. A striking observation was made on eye colour. The male twin had one green-brown

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