tion, *H. influenzae* meningitis, is less imperative in view of such results as those of F. F. Barrett and colleagues,[12] who obtained an at least equally good effect with ampicillin. Other common forms of meningitis respond better to penicillin. Of respiratory tract infections almost any can be treated satisfactorily in other ways except a severe exacerbation of *H. influenzae* bronchitis in an elderly patient and possibly severe pertussis in a young baby. Rickettsial and viral infections are at least equally susceptible to treatment with tetracyclines. For staphylococcal infections there is now a wide choice of other antibiotics considerably more active than chloramphenicol. For urinary tract infections there is also a much wider choice of other drugs than formerly, and chloramphenicol is at a disadvantage for this purpose because about 90% of the dose is excreted in a conjugated and inactive form. The recent studies of A. A. Lindberg and his colleagues[13] have shown that in the presence of renal insufficiency so little active chloramphenicol may be excreted as to render an adequate effect in the urine most improbable. Some of these verdicts may be disputed, and different clinicians may have particular uses for chloramphenicol to which they attach importance, but if it were always given only "when no other antibiotic will suffice" the occasions for prescribing it would be few and far between.

Refsum's Disease

It cannot be maintained that "heredo-ataxia hemeralopia polyneuritiformis" or "heredopathia atactica polyneuritiformis" (Refsum's syndrome), and "3, 7, 11, 15 tetramethyl decanoic acid" or "hexadecanoic acid" (phytanic acid) are euphonious contributions to clinical medicine. Nevertheless, a fascinating relationship exists between the disease and the acid.

In 1946 S. Refsum[1] described a new and bizarre neurological disease in five members of two unrelated families, and at first this disorder was considered to be a variety of hereditary ataxia. Refsum's observations, which provoked several reports of similar cases,[2–4] established the identity of the disease and led to acceptance of four cardinal diagnostic signs—namely, chronic polyneuropathy, cerebellar ataxia, atypical retinitis pigmentosa, and an increased protein content of the cerebrospinal fluid. Other abnormalities that have been found in some patients have included anosmia, changes in pupillary reactions, neurogenic deafness, cardiomyopathy,[5] skin changes resembling ichthyosis, and skeletal abnormalities. J. Cammermeyer,[6] who investigated Refsum's original cases, concluded that the basic neuropathological change was in the myelin sheath and was identical with the lesions of hypertrophic neuropathy of Déjerine and Sottas. Detailed necropsy studies in a recent case report[7] have attributed the thickening of the peripheral nerves to two principal factors—firstly, the accumulation of an exudate beneath the nerve bundles and the perineurium, and, secondly, an increase in the amount of fibrous tissue surrounding the axons. The exudate was eosinophilic, and contained stainable lipoid in droplet form. Diffuse fibrosis was present in the myocardium, and many fat vacuoles were present in the liver and kidneys.

Awareness of this curious neurological disease would have been justifiably limited—a rare specimen for collectors of uncommon diseases, or a burden to the memories of weary Membership candidates—if E. Klenk and W. Kahlke[8] had not demonstrated the presence of high concentrations of phytanic acid in the blood and tissues of affected patients. Other workers, moreover, were soon able to confirm excessive storage of phytanic acid in the liver, kidney, skeletal muscles, and urine of affected patients. Thus this discovery of a biochemical abnormality in a chronic neurological disease with a gloomy prognosis offered exciting possibilities for the eventual treatment of the syndrome.

Phytanic acid was first discovered in butter fat,[9] and subsequently in ox plasma[10] and perinephric fat.[11] It has been synthesized from phytol—a constituent of the chlorophyll molecule—and it has been found to accumulate in the liver and plasma of rats fed on phytol. This suggests that dietary chlorophyll, butter, and animal fats may be the exogenous precursors of phytanic acid. Phytol is normally oxidized to carbon dioxide, and it has been postulated that in Refsum's disease a genetically determined defect (perhaps enzymatic) is responsible for a failure of oxidation—with the result that phytanic acid is incorporated into the developing myelin. Recently L. Eldjam and his colleagues[12] have reported the effects of a diet containing only minimal amounts of phytanic acid in two patients with Refsum's disease. The level of phytanic acid in the serum fell, and in one patient clinical improvement occurred. This demonstration that Refsum's disease is a disorder of lipid metabolism which may be influenced by changes in the diet is an extremely encouraging and welcome advance in the biochemical exploration of inherited neurological diseases, and many people will look forward to further progress in this field.

Immunosuppressive or Anti-inflammatory?

Alkylating agents and antimetabolites are capable of blocking the synthesis of deoxyribonucleic and ribonucleic acids at a number of points along the metabolic pathways.[1] Because they thus inhibit the proliferation of malignant cells, they have played an important part in the treatment of cancer. They have also been shown experimentally to inhibit the primary and secondary antibody responses to antigenic stimulation,[2] and they can delay the rejection of homografts.[3] The next step was naturally to explore the use of drugs with these properties in treating diseases thought to result from abnormal immune responses. Now some encouraging results with "immunosuppressive therapy" have been reported in systemic lupus erythematosus,[4 5] autoimmune haemolytic anaemia,[6] "lupoid" hepatitis,[7] "lipoid" nephrosis,[8] and proliferative glomerulonephritis.[9]

In a recent report on azathioprine therapy in "autoimmune" diseases C. C. Corley, H. E. Lessner, and W. E.

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12 Eldjarn, L., *et al.*, *Lancet*, 1966, **1**, 691.

Larsen[10] noted improvement in 16 out of 34 cases. The patients had a variety of disorders, including chronic idiopathic thrombocytopenic purpura, systemic lupus erythematosus, nephrotic syndrome, haemolytic anaemia, and Goodpasture's syndrome. The observation that platelet counts in four out of seven cases of thrombocytopenic purpura rose during treatment is of interest, since toxic depression of normal levels is a recognized hazard of treatment.[9 10] W. E. Grupe and W. Heymann[11] have also reported improvement, in selected children suffering from steroid-resistant renal disease, after treatment with azathioprine, cyclophosphamide, or chlorambucil. In discussing the mode of action of cytotoxic drugs in "autoimmune" diseases these workers refer not only to the suppression of immune responses but also to the anti-inflammatory effect which has been observed in rabbits,[12] suggesting that both may play a part.

That the small lymphocyte has a role in immune mechanisms is undisputed. Sir Macfarlane Burnet has suggested that its main function is "the carriage of immunological information."[13] The diminished intensity with which lymphocytes infiltrate tissues under the influence of cytotoxic agents is interpreted as evidence that the retardation of homograft rejection observed in man,[3] and of the onset of autoimmune glomerulonephritis in susceptible mice,[14] is due to the suppression of immune responses. On the other hand, C. D. West and colleagues found cyclophosphamide to be less effective in the treatment of persistent hypocomplementaemic glomerulonephritis[15] than in "lipoid" nephrosis.[8] In the hypocomplementaemic disease the lowered levels of serum beta-1c-globulin and the presence of immune globulin deposits in glomeruli are evidence of immunological disturbance,[15 16] while in "lipoid" nephrosis there is no such evidence.[17] From these findings it is possible to argue that the action of the drugs is not immunosuppressive but anti-inflammatory. Indeed, A. R. Page and colleagues[7] showed that the normal mononuclear inflammatory response to skin injury in patients receiving 6-mercaptopurine was diminished or even abolished, while delayed hypersensitivity to old tuberculin and other antigens in the same patients was unaltered. In the case of proliferative glomerulonephritis direct interference with the metabolism of glomerular cells has been suggested as possible,[9] but, though occasional mitoses have been reported in proliferating endothelial cells,[18] their rate of division is unlikely to match that of, say, leukaemic cells, and this mode of drug action seems improbable.

Suitable experiments are needed to obtain answers to these pharmacological problems, and for the time being the use of cytotoxic drugs must remain empirical. However, the encouraging results so far reported in treating a group of diseases for which corticosteroids have proved disappointing must surely justify continued investigation into their use, provided that we do not lose sight of the dangers of too willingly accepting potentially toxic drugs whose value has not yet been proved in an adequately controlled trial. The comparatively small series of cases treated with these drugs so far must be regarded as pilot studies. Evidence of previous resistance to corticosteroids is in itself not proof that cytotoxic drugs are superior, for the drugs have been given to the same patients *at different times*. It therefore seems essential, as has previously been suggested,[19] to establish controlled trials. C. C. Corley and colleagues[10] have shown that it is not difficult to collate information obtained in a number of collaborating centres.

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Frozen Section in Surgery

The advantage of the frozen-section technique for examining tissues removed during operation is that it enables a diagnosis to be made in less that 15 minutes, whereas with conventional techniques using paraffin sections this would take two days. Nevertheless, frozen-section methods have the serious disadvantage of producing thicker sections which are less easy to interpret. This inevitably results in some wrong diagnoses, but this danger has been considerably reduced since the introduction of the cold microtome in a cryostat cabinet.[1] With this method it is possible to cut sections as thin as those from paraffin blocks, and to make a diagnosis within 7 to 15 minutes of excision of the lesion.[2]

The extent to which the frozen-section method can be used depends on the capacity of the laboratory to cope with the work. As L. V. Ackerman and G. A. Ramirez have emphasized, the basic purpose of frozen-section diagnosis is to make a therapeutic decision at the time of operation.[3] It is of great value in those instances where a diagnosis of malignancy would necessitate a large resection, whereas a benign lesion could be dealt with by local excision. If a radical resection is performed immediately after the diagnosis has been established there is probably much less likelihood of lymphatic and blood-borne dissemination of tumour cells than there would be if a diagnostic biopsy preceded resection by several days. When possible the lesion should be completely excised before diagnosis in order to prevent the opening-up of vascular channels, through which tumour cells might be disseminated, and to obviate the risk of their implantation in the wound.

It is in the diagnosis of swellings of the breast that the frozen-section method finds its greatest use. Not only are these lesions very common, but they are also often difficult to diagnose both clinically and macroscopically. S. B. Desai has recently reviewed 1,006 consecutive frozen section diagnoses of mammary lesions performed at the Royal Marsden

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