signs, and the discovery of local tenderness on rectal examination could be diagnostic.

Though urinary examination must be carried out in every acute abdominal emergency the results may be misleading. P. H. Smith[5] has shown that red cells or pus cells or both are fairly common in the urine of patients with acute appendicitis. Winsey and Jones found that four of the children with appendicitis had pus cells in the urine. A careful study of plain radiographs of the abdomen by a skilled radiologist may be of help in diagnosis. Indeed, D. W. Brooks and D. A. Killen[6] have described no fewer than nine *x*-ray signs, which include a faecalith in the right iliac fossa, gas outlining the lumen of the appendix, and local blurring of soft tissues. However, many of these signs are non-specific and represent merely an inflammatory process in the right iliac fossa. In fact a few patients in their series had positive *x*-ray signs without any pathological lesion being discovered at operation.

It is therefore apparent that in the diagnosis of appendicitis, especially in childhood, clinical alertness is of the utmost importance. Mason Brown's aphorism that "in any child with acute abdominal symptoms the doctor should think first of acute appendicitis, no matter how young the child may be" is advice of gold.

Toxicity of Chloramphenicol

For fifteen years the profession has been "divided into those who, perhaps having seen chloramphenicol cause marrow aplasia, fear this effect and rarely use the drug, and a larger number who ignore this possibility because it seems too remote and prescribe chloramphenicol freely."[1] It seems from the paper by Dr. T. W. Meade at page 671 of the *B.M.J.* this week that this division follows no line related to education or accomplishment. Indeed it might well be found to separate those of consultant rank as well as general practitioners into two camps. This strange and usually silent division of opinion and practice has now existed ever since marrow aplasia was first recognized as a consequence of chloramphenicol treatment. From time to time it breaks into public controversy, and this has happened again with the issue of a statement by the Committee on Safety of Drugs.[2] It recommends that except for treating typhoid fever or *H. influenzae* meningitis, this antibiotic "should not be used systemically except when careful clinical assessment, usually supplemented by laboratory studies, indicates that no other antibiotic will suffice."

Prescribing of chloramphenicol in Great Britain seems to be on a much more moderate scale than in the United States. In a survey of the use of antimicrobic drugs in hospitals in and around Philadelphia H. A. Reimann and J. D'Ambola[3] found that 0.84 kg. per month was being used in a teaching hospital, and mention five others in which chloramphenicol accounted for a large proportion, up to one-half, of all the antibiotics prescribed. Meade's 182 doctors issued an average of only 8.5 prescriptions for it in a month. The Drug Safety Committee's statement refers to 24 known cases of marrow aplasia in a period when 1,000,000 prescriptions were issued plus an unknown number in hospitals. This means that our average prescriber would encounter marrow aplasia only once in at least 500 years of practice, a risk which he may be prepared to take. Most large-scale surveys have produced similar results, though K. M. Smick and his colleagues[4] acknowledge that their figure of 1 in 60,000 cases treated in California is for stated reasons certainly an underestimate.

If this complication is so rare, why have some authors seen not merely single cases but series? W. Dameshek[5] saw four in a single month; R. G. Shaw and J. A. McLean[6] saw seven in 12 months in Melbourne, and D. W. O'G. Hughes[7] reports 16 in eight years in a children's hospital in Sydney. Are Australian bone marrows peculiarly vulnerable? By way of contrast, according to A. M. Walter and L. Heilmeyer[8] no case has ever been reported in a native of West Germany. If the true incidence is higher than national surveys suggest, is it that the diagnosis of aplastic anaemia can sometimes be missed, or, if made, is there failure to relate it to its cause? The interval between medication and the onset of aplastic anaemia is commonly 1 to 3 months, and may be as long as 9 to 12 months.[9]

To discover why this usually fatal complication should affect some patients both a clinical and an experimental approach are possible. On the clinical side there is evidence of enhanced danger from prolonged or repeated courses, but some affected patients have had, so far as is known, only a single short course. Could the missing factor be the simultaneous administration of another drug, possibly innocuous when given alone? Three patients who died of agranulocytosis attributed to sulphapyridine were later discovered by G. Discombe[10] also to have been given proprietary sedatives containing amidopyrine. Here presumably two potentially myelotoxic drugs acted synergically, but could some other drug, not in itself myelotoxic, potentiate the action of chloramphenicol on the marrow? This is a hypothesis which could easily be tested experimentally. It is notoriously difficult to produce the full picture of aplastic anaemia with chloramphenicol in animals, but by the study of lesser abnormalities of erythropoiesis could not more information be got about the influence of previous medication on the effects of a second course? The precise effects of original dose and time interval are unknown and cannot be deduced from miscellaneous and imperfect case records. L. P. Garrod[11] suggested as another perhaps remote possibility that small amounts of chloramphenicol ingested in milk from cows treated for mastitis may sensitize the marrow to subsequent therapeutic administration. Experiment could also refute or establish this possibility.

If no further light can be thrown on this problem, and the verdict of the Drug Safety Committee is accepted and acted on, what uses for chloramphenicol remain? Typhoid fever is an absolute indication, as is exceptionally severe salmonellosis of other types, but all other intestinal infections can be treated adequately with other drugs, if indeed they need specific drug treatment at all. The second stated indica-

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[2] *Brit. med. J.*, 1967, **1**, 484.
[3] Reimann, H. A., and J. D'Ambola, *Arch environm. Hlth*, 1966, **13**, 631.
[4] Smick, K. M., Condit, P. K., Proctor, R. L., and Sutcher, V., *J. chron. Dis.*, 1964, **17**, 899.
[5] Dameshek, W., *J. Amer. med. Ass.*, 1960, **174**, 1853.
[6] Shaw, R. G., and McLean, J. A., *Med. J. Aust.*, 1957, **1**, 352.
[7] Hughes, D. W. O'G., ibid., 1962, **2**, 251.
[8] Walter, A. M., and Heilmeyer, L., *Antibiotika Fibel*, 2nd ed. Stuttgart. 1965.
[9] Sharp, A. A., *Brit. med. J.*, 1963, **1**, 735.
[10] Discombe, G., ibid., 1952, **2**, 1270.
[11] Garrod, L. P., *Practitioner*, 1965, **195**, 36.
[12] Barrett, F. F., Eardley, W. A., Yow, M. D., and Leverett, H. A., *J. Pediat.*, 1966, **69**, 343.
[13] Lindberg, A. A., Nilsson, L. H.son., Bucht, H., and Kallings, L. O., *Brit. med. J.*, 1966, **2**, 724.

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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