follows the intern year, with all its fateful consequences for frustration among young hospital doctors. Certainly if some of the leading recommendations of the Royal Commission on Medical Education[3] are ever to be put into effect much more than quiet nods of assent will be needed from the Royal Colleges. The surgeons have pushed ahead, and their plan will be widely welcomed.

Trimethoprim

In 1962 B. Roth and colleagues[1] described fully a series of synthetic compounds, including the antimalarial drug pyrimethamine and a potent antimicrobial, trimethoprim (2,4-diamino-5-(3′,4′,5′-trimethoxybenzyl)-pyrimidine). This substance acts with sulphonamides in a synergic and bactericidal manner. In a recent report J. H. Darrell, L. P. Garrod, and Pamela M. Waterworth[2] say they believe the drug "to represent a major discovery and to have far-reaching therapeutic possibilities."

Trimethoprim inhibits competitively the enzyme dihydrofolic acid reductase, which converts dihydrofolic acid to tetrahydrofolic acid, a stage in the synthesis of purines and ultimately of D.N.A. This stage is preceded by the incorporation of para-aminobenzoic acid into dihydropteroate, a reaction which is competitively inhibited by sulphonamides. It is because they have such closely related actions that trimethoprim and sulphonamides are strongly synergistic antimicrobial compounds. Trimethoprim has been found to have negligible effect on the mammalian as distinct from the bacterial enzyme, and there is little indication of interference with folate metabolism when the drug is given to animals or man.

The earliest clinical reports on trimethoprim[3–5] refer to the successful treatment of *Proteus* septicaemias and urinary, lung, and skin infections. More recently there have been accounts of its efficacy in the treatment of gonorrhoea[6] and bronchial infections.[7 8] Darrell, Garrod, and Waterworth[2] suggest that the best combination for clinical use is with sulphamethoxazole (Gantanol), since their rates of appearance in and disappearance from the blood when given by mouth are similar. In vitro, sulphafurazole (Gantrisin) was used for its greater solubility. The combination was found to be bactericidal, an observation which suggests the possibility of its use in the treatment of septicaemias and subacute bacterial endocarditis, for which conditions the bacteriostatic sulphonamides are normally considered inappropriate.

Trimethoprim was found to be active against a wider range of organisms, and in lower concentration, than sulphonamide alone. Determination of the minimum inhibitory concentration of the combined drugs showed, in almost all experiments with organisms sensitive to both, a high degree of synergy and an increase in efficacy, so that an ineffective concentration of one drug reduced the M.I.C. of the other usually eightfold, sometimes more. This applied to a range of bacteria, including *Streptococcus pneumoniae, Str. pyogenes, Neisseria gonorrhoeae, Escherichia coli, Shigella* spp., *Proteus* spp., and *Pseudomonas aeruginosa,* and to a somewhat lesser extent to *Staphylococcus aureus, Haemophilus influenzae, Salmonella* spp., and *Klebsiella* spp.

The combination of drugs appears to inhibit the rapid acquisition of resistance to trimethoprim seen in organisms grown in increasing concentrations of it, a point possibly of great clinical importance. Clinical bacteriologists will wish to refer to this paper for details of routine combined sensitivity tests and media suitable for the performance of such tests.

Enough is now known about this important therapeutic combination to justify extended clinical studies, especially in cases of urinary and chest infections, Gram-negative septicaemia, and perhaps staphylococcal infections. The combination is expected to have a wider range of antibacterial action and to be more effective therapeutically than sulphonamides alone in the treatment of infections with sulphonamide-sensitive organisms. The bactericidal properties of the combination may give it an important role in the treatment of septicaemias and other life-threatening infections not normally treated with sulphonamides.

Anonymous Mycobacteriosis

There is a well-known but ill-understood relationship between disseminated tuberculosis and some severe blood disorders, and this has reappeared in a new form with reports of rather similar haematological abnormalities in patients with disseminated infections by anonymous mycobacteria. T. M. Kilbridge, J. S. Gonnella, and J. T. Bolan[1] have recently described two patients with pancytopenia (particularly affecting the neutrophils) in whom mycobacteria were demonstrated histologically post mortem, and from one of whom a photochromogen was cultured.

Kilbridge and his colleagues reviewed 16 previously reported cases of disseminated anonymous mycobacteriosis, characterized by a long fluctuating illness with poor response to antituberculous therapy and an almost invariably fatal outcome. About half the patients had miliary pulmonary infiltration, pneumonia was common, and anonymous mycobacteria were frequently recovered from the sputum or from biopsies of bone marrow, spleen, liver, or lymph nodes. In five children with Batty bacillus infections multiple osteolytic lesions suggestive of a reticulosis were present. All 11 patients in which haematological data were studied were anaemic, 7 severely so; 5 had neutropenia, and 5 had granulocytic hyperplasia, myeloproliferative disorders, or myeloid leukaemia.

These cases resemble those described in relation to tuberculosis,[2 3] and the same difficulties arise in deciding whether the infection is the cause or the result of the blood disorder. Many of the patients with disseminated mycobacteriosis had severe underlying diseases, including Hodgkin's disease or lymphosarcoma, and many had received immunosuppressive agents or radiation. In a number coexistent fungus diseases were found at necropsy, suggesting that disturbance of the patient's immune mechanisms was responsible for the overgrowth of mixed opportunists, including mycobacteria.

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