us,[2] the most significant factor affecting the production of myoedema is the thickness of the muscle and the overlying soft tissues rather than the underlying disease state. Owing to the unpredictability of this sign, and the wide range of normality, it is doubtful whether it can ever be utilized as a reliable or useful bedside sign.—I am, etc.,

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Trimethoprim for Malaria

SIR,—Your excellent note on trimethoprim in Today's Drugs (6 September, p. 578) omitted mentioning the value of this compound for treatment of *P. falciparum* infections resistant to 4-aminoquinolines (chloroquine and amodiaquine).

A report by Martin and Arnold[1] indicated that trimethoprim in combination with sulfalene (3-methoxy-2-sulfanilamidopyrazine) can cure falciparum malaria in man. Both drugs are antagonistic in the synthesis and metabolism of folic acid, and have a potentiating or at least an additive effect on the dihydrofolate reductase.[2]

Experimental work on the simian *P. knowlesi* malaria indicates the mode of action of this drug combination.[3] It is interesting that trimethoprim alone is relatively ineffective against acute infections of *P. berghei* in mice or *P. knowlesi* in rhesus monkeys while rather more effective against the human *P. falciparum*.—I am, etc.,

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Extra-articular Manifestations of Rheumatoid Arthritis

SIR,—Dr. A. Calin is quite right (6 September, p. 598). Anaemia is certainly a very common manifestation of rheumatoid arthritis. It is so common, however, and has such a large literature devoted to it that I did not discuss it, as in the limited time of a college lecture—one hour—deletions have to be made in any large subject. Other extra-articular manifestations are those arising from bursae, tendons, bones, and mental states such as depression and anxiety, all of which contribute to, and play a part in, rheumatoid disease, and none of which did I attempt to discuss for the same reason.

Haematological features are well recognized in rheumatoid arthritis, and the changes of Felty's disease, for instance, are discussed in all comprehensive textbooks of haematology. From the Edinburgh unit alone a large amount of excellent work has emerged in the last few years on the nature of anaemia in rheumatoid arthritis.[1] For this reason, particularly, I did not discuss it, as it had already been so fully discussed, but Dr. Calin is very right in drawing attention to its frequency and its importance, particularly in relation to therapy.

The extra-articular manifestations of rheumatoid arthritis comprise such a large subject that one could readily do another hour's lecture—a Part II, as it were—on the same theme, without re-covering any ground covered by the previous one.—I am, etc.,

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REFERENCE

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SIR,—Dr. A. Calin (6 September, p. 598) is hardly fair to Dr. F. Dudley Hart (19 July, p. 131) in expecting him to discuss the very complex problem of the anaemia of rheumatoid arthritis in his Philip Ellman lecture. The anaemia associated with this condition is so common that it hardly merits consideration alongside the rarer extra-articular manifestations of the disease which were the subject of this lecture. In addition, Dr. Calin is less than fair to a large number of investigators when he says "very little is known about the aetiology of this anaemia." In particular, since 1955 a succession of workers in the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh, have published over a dozen papers on various aspects of iron metabolism and the normocytic, hypochromic anaemia in rheumatoid arthritis, quite apart from several contributions to the understanding of the associated but less common megaloblastic anaemia. Most of these papers have appeared in the *Annals of the Rheumatic Diseases*, and the present state of our knowledge has been summarized.[1]

The mechanisms involved in the causation of this anaemia are numerous. Minor factors are a mild impairment in the absorption of iron from the gastrointestinal tract; a mild extra-corpuscular haemolysis; a small increase in plasma volume; a failure of the bone marrow to increase red cell production above normal levels because of reduced erythropoietin activity whether due to a failure of production or the presence of an inhibitor or antibody; that in the presence of a low serum albumin the incorporation of iron into new erythrocytes is impaired; an increased rate of degradation of transferrin, and a diminished release of endogenous iron from senescent red cells. The importance of blood loss from the gastrointestinal tract induced by salicylate and other drug therapy as a cause of the anaemia has been exaggerated.[2 3]

The major factor in the aetiology of this anaemia is the increased uptake and failure of release of iron by the hyperplastic reticulo-endothelial system and the phagocytic cells of the proliferated synovial tissue. Calculations suggest that as much as 800 mg. of iron may be stored in the synovial tissue of a patient with active rheumatoid arthritis.

Most of these abnormalities of iron metabolism are well correlated with the activity of the disease. Indeed, it has been postulated that the serum iron value is the best indicator of disease activity.[4 5] Thus if the disease is controlled the hypochromic, normocytic anaemia can be corrected without the addition of any haematinic.[5] Correction also may be achieved if large quantities of parenteral iron are administered, as, unlike oral therapy, this allows sufficient iron for new erythrocyte production to bypass the overactive reticulo-endothelial system and synovial tissue. The best results are achieved when a combination of these methods is used.[6]—I am, etc.,

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G.M.C.'s Annual Levy

SIR,—Although I have been a member of B.M.A. for the last four years, unfortunately I failed to take note of the subject of a leading article in the *B.M.J.* (3 May, p. 266) and correspondence and reports of meetings, all purporting to inform the like of us the news of a new "levy" on the profession. I, of course, refer to the decision of the General Medical Council to charge members of the profession an annual fee for the privilege of being on the *Register*. This came to me as an unexpected blow, and many of my colleagues seemed to react with a similar sense of surprise and unawareness. But the surprise turned into a feeling of frustration and betrayal when it was learnt that B.M.A. had negotiated with G.M.C. (from 1965 when the subject was first brought up), and agreed acceptance on behalf of the profession of an annual retention fee, the amount of which is to be determined.

Already I find it difficult to understand the logic of the annual taxes that one has to offer to the royal colleges (heaven help you if you are a Fellow or member of more than one college!). However, it may still be argued in their favour that they are offering a continuing service in the form of refresher courses, regional lectures and demonstrations (although not always free), and also facilities (library, etc.) on the college premises. But can one clearly define the kind of services the G.M.C. is going to provide which would require adding to its present annual income of £145,000 an estimated £130,000 to £195,000 per year, if each of Britain's 65,000 doctors are charged £2 to £3 per year?

But of course we must face realities. The G.M.C. is not a profit-making body, and if it needs money it has got to have it. However, I don't agree that the State should not be asked to provide the grants to this indepen-