policy still right in principle then? Or is there a risk that the patient may fall between two stools, for lack of what Job describes as a "daysman"?

Experience indicates that this dilemma can and does result in major and minor tragedies: like that of the schoolmaster with "consolidation of the left lower lobe" who presented in the chest ward three months later with an inoperable bronchial carcinoma; like the farmer with "fibrosis in the right upper lobe" whose sputum was positive; like the man with "an interesting x-ray; suggest repeat in three weeks" whose right upper lobe carcinoma was even then producing superior vena caval obstruction; like the man with "an interlobar effusion" whose malignant abscess was inoperable; like the two child contacts whose several x-rays showed "only catarrhal changes" but who had never been tuberculin-tested; like the middle-aged anxious lady who had to be seen urgently at the chest clinic because her x-ray showed "tuberculous disease at the right apex" and who needed much reassurance that it was a soundly healed calcified scar of no clinical significance. And then one recalls the men with haemoptyses and "clear chest x-ray" reports, who nevertheless had inoperable proximal carcinomata; to say nothing of the semi-crippled asthma or bronchitis patient whose x-ray shows "nothing more than slight emphysema and bronchitic changes."

Doubtless one sees an unhappy selection of latecomers in hospital chest practice; and doubtless one is also influenced by the geographical implications of their previous lengthy ambulance trips to and from the x-ray department; but the fact remains that patients needing chest x-rays frequently also need a proper clinical and ventilatory assessment—and in these circumstances there is much to be said for the "open door" chest clinic rather than the "open door" x-ray department.—I am, etc.,

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Alopecia and Cytotoxic Drugs

SIR,—The unfortunate epilating effect of cyclophosphamide and of thiotepa to which Mr. W. Calvert refers in his letter (1 October, p. 831) is shared by several other cytotoxic drugs.

According to Wiltshaw,[1] practically every alkylating agent when given in large enough doses will produce alopecia. Alopecia probably occurs more frequently with vincristine, cyclophosphamide, and 5-fluorouracil than with other agents. Vincristine produced alopecia in 42% of a group of children with acute leukaemia reported by Evans *et al.*,[2] in 46% of 26 patients reported by Carey *et al.*,[3] and in 65% of 44 patients with advanced malignant disease reported by Whitelaw *et al.*[4] Cyclophosphamide's epilating effect was apparent in 11.5% of Betteridge's 52 patients[5] and 60% of Anders's cases,[6] but reported incidences of cyclophosphamide alopecia have varied from nil to 100%. Bell[7] found 5-fluorouracil caused alopecia in 10% of his 64 patients with carcinoma of the bladder, colon, stomach, and pancreas.

Occlusion of the blood supply to the scalp during and for five minutes after injection of a potentially epilating drug will, according to several unpublished reports, prevent or reduce to insignificant proportions the incidence and extent of hair loss. A special narrow sphygmomanometer cuff for scalp occlusion (available from Charles F. Thackray Ltd., of Leeds) is applied before the injection and inflated to a pressure above systolic, which is maintained until five minutes after the injection. During this period the blood level of the drug falls as it is taken up by liver, tumour, marrow, and other tissues, and on release of the tourniquet the concentration in the blood reaching the scalp is not high enough to interfere with the functional integrity of the hair follicle.—I am, etc.,

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SIR,—I read with interest Mr. W. Calvert's report of the loss of a good deal of hair after thiotepa (1 October, p. 831).

Whereas I have little experience of the use of thiotepa I have been using cyclophosphamide (Endoxana) as a routine primary treatment for carcinoma of the breast for the last three years. My practice is to give a test dose of 100 mg. intravenously two days before operation and 500 mg. intravenously daily for five doses from the day before operation. I combine this with a Patey modified radical mastectomy and in premenopausal women a bilateral oophorectomy. In addition radiotherapy is given as advised by consultation with the regional radiotherapy department (to whom I am grateful for much helpful advice). Leucopenia and feeling generally unwell are not uncommon side-effects, but nothing like as distressing to the patient as the complete alopecia that sometimes occurs.

For the last 12 months I have been using an inflatable tourniquet around the head, pumped up to 10 mm. Hg above the systolic pressure immediately before the injection is given and kept so for five minutes. There continues to be some hair loss, but I have had no instances of complete alopecia since.

Rather curiously I have had no cases of alopecia in patients for whom we have used cyclophosphamide intraperitoneally, as in ovarian carcinoma, for instance. If Mr. Calvert is meeting alopecia in cases where intraperitoneal thiotepa is used, it would not be reasonable to maintain scalp ischaemia to the degree I have used it for intravenous therapy for a sufficient length of time.

Partial ischaemia might be maintained, however, for a longer period, perhaps 3–4 hours, by asking the patient to wear a rather tight-fitting bathing cap following the intraperitoneal administration.—I am, etc.,

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Disease Spectrum in Arthritis

SIR,—We appreciate Dr. Wood's thoughtful comments (8 October, p. 887) on our letter, but we should like to remove a misunderstanding concerning methodology.

We have found[1–4] that the sex- and age-distribution of a wide variety of diseases and ageing conditions such as chronic discoid lupus erythematosus, systemic lupus erythematosus, Raynaud's disease, systemic sclerosis, coronary heart disease, diseases of the mitral valve, manic depressive psychosis, schizophrenia, involutional psychosis, diabetes mellitus, greying of hair, clinical dental caries by tooth type, mortality of permanent teeth by tooth type, Dupuytren's contracture, Bell's palsy, Huntington's chorea, petit mal, grand mal, duodenal ulcer, gastric ulcer of the body, gastric ulcer of the antrum, ulcerative colitis, myasthenia gravis, polycythaemia vera, Hodgkin's disease, and psoriasis are consistent with three generalizations: (1) When the disease is confined to one or more sub-populations, the specificity of such groups is determined by genetic factors. (2) The disease process is initiated in genetically predisposed individuals through the occurrence of one, or a small number, of highly specific random events. These events have some remarkably simple properties.[1–4] (3) An interval or latent period elapses between the last initiating event and the symptomatic or clinical onset of the disease. Two main types of latent period characteristics have been observed, both with simple properties.[1–4]

We conclude, therefore, either that we have encountered a large series of gigantic coincidences and that the sex- and age-distributions of the above, and many other diseases, have no pathogenetical and aetiological significance, or that (1), (2), and (3) describe, more or less accurately, fundamental biological laws of wide generality. To adopt the first alternative would be to repudiate the scientific method, and therefore we incline to the second.

No *a priori* assumptions were made about the homogeneity of the mechanisms leading to radiological erosive arthritis (E.A.) and clinical inflammatory polyarthritis (I.P.), and we examined their sex- and age-distributions for conformity with (1), (2), and (3). We concluded (6 August, p. 362) that these are "relatively homogeneous" diseases—unlike rheumatoid arthritis diagnosed by the American Rheumatism Association criteria, which appears to us, and evidently to Dr. Wood and others, to be a complex of distinctive disease processes and conditions.

We have already referred (6 August, p. 362) to the specificity of joint attack in E.A. and I.P., and Dr. Wood has further elaborated this point, but there is another aspect of possible heterogeneity within E.A. which we should emphasize. It might resolve the apparent contradictions described by Dr. Wood between the age patterns and the familial studies of E.A. The curves of the age-specific prevalence of grade 1+ E.A. for all sites, cervical spine, and hands and feet,[5] against age, actually show an initial flat portion. The flat portion of the curve for all sites occurs at just under 20% (population prevalence) from 15 years (the lowest age group examined) up to about 30 years of age. This could be accounted for in one of at least three ways: (i) it corresponds to the average percentage of randomly distributed false-positive diagnoses; (ii) it represents a genuine form of E.A. with high penetrance (approaching 100% by 15 years of age)