number of patients with normal, or complicated pregnancies, and with leukaemia, we have found a persistent non-specific agglutination despite repeated reabsorption with sheep red cells and as a consequence the F.D.P. immunoassay is not possible with these specimens. Dr. Cash's finding of a substantial variation in the ability of sheep cells to absorb sheep-red-cell haemagglutinins may be part of the explanation for the persistent non-specific agglutination in these cases. Our findings as presented in Fig. 1 have been misinterpreted by Dr. Cash when he assumed that in 46% of our patients no serum F.D.P. was detectable after the thirtieth week of pregnancy. We stated in our report that the F.D.P. immunoassay with sheep cells was reproducible down to a level of 1 μg/ml. By employing higher dilutions of the antisera the maximum sensitivity is further increased, but we have found that reproducibility is greatly impaired when very dilute antisera are used.

The difference in our findings during pregnancy may be more simply explained by the range of normal values for serum F.D.P. which in Dr. Cash's study of pregnant women was from 3 to 34 μg/ml. in the third trimester with approximately 40% of the patients in the normal non-pregnant range. A better assessment of the changes in the F.D.P. level during pregnancy is likely to be obtained by serial observations on a group of women from early pregnancy to term, using human group O cells for the assay to eliminate the problem of anti-sheep red cell agglutinins in human serum.

We do not quite share Dr. Cash's enthusiasm for busy routine laboratories to undertake the immunoassay for F.D.P.s. Laboratories equipped to investigate haemostatic problems may indeed find the assay of value; F.D.P. assays in isolation are unlikely to be of any value without further information as to the clotting mechanism and the levels of the components of the fibrinolytic system. We have in mind the particular danger that elevated levels of F.D.P. might be erroneously interpreted as representing pathological proteolytic activity, and an indication for the use of fibrinolytic inhibitors.—We are, etc.,

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Analgesic Nephropathy

SIR,—We are sorry that our article on analgesic nephropathy (16 August, p. 378) has confused Dr. J. H. Shelley (20 September, p. 720) since we do not think the issues are as clouded as he suggests. We were careful to emphasize that the stabilization or improvement of renal function illustrated in Fig. 5 occurred after the initial effects of rehydration, etc., had been assessed. We believe there is a strong case for attributing this improvement to drug withdrawal: if so, which is the important drug?

We specified phenacetin withdrawal in our title because this was the only drug which all our patients were taking when they were deteriorating, and which all had withdrawn when they were improving. Of course, doubt must remain about the role of the other ingredients in the mixtures consumed by these patients, and by those in other reports. However, the practising physician cannot wait for final proof; he must make an interim judgement and advise his patients. Those who have already advanced renal damage cannot afford to take risks with their few remaining nephrons. We believe that such patients should be advised to avoid all analgesics on which any suspicion of nephrotoxicity rests, and this must at the present time include salicylates and paracetamol. However, when we advise the more numerous patients with normal kidneys who require analgesic therapy we need firmer ground before rejecting aspirin in favour of its effective alternatives, none of which is free from side-effects.

Dr. Bengtsson[1] has convincingly marshalled the evidence that it is phenacetin, not aspirin, that is commonly the cause of nephrotoxicity. Dr. Shelley protests that nephropathy is rare when phenacetin is consumed by itself, but how often is this drug prescribed alone? We have questioned numerous colleagues; none admits having ever prescribed phenacetin alone and most are unaware that it is available. Contrast this with the vast quantity of aspirin consumed on and off prescription. The rarity of pure aspirin nephrotoxicity will surely have much greater significance than the rarity of pure phenacetin nephropathy. We suggest that nephropathy almost always occurs after consumption of drug mixtures, because phenacetin is nearly always consumed in this form. We retain a sufficiently open mind to continue calling this condition "analgesic nephropathy," but when we get headaches we take soluble aspirin.—We are, etc.,

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REFERENCE

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Malignant Granuloma

SIR,—Your leading article on malignant granuloma (2 August, p. 254) has attracted a great deal of clinical attention.

The pathologist called on to advise on the lesion causing non-healing prolonged nasal or palatal ulcerations has a difficult path to tread. Briefly, a long list of more or less well-defined specific granulomata, as well as neoplasia, has to be eliminated. There seems to exist a certain amount of confusion owing partly to the fact that the non-healing granuloma, as a clinical entity, is a group of two, possibly three, pathological entities.[1]

The classical or Stewart type, usually lethal form of ulceration—localized in the upper respiratory tract—may respond to radiotherapy.[2] Histopathologically, it consists of non-specific granulation tissue of pleomorphic character. It is in such a case, where the discrepancy between the highly dramatic clinical picture and the comparatively trivial histopathological findings of inflammatory granulation tissue may cause considerable diagnostic difficulty. The patient referred to in Mr. Maxwell Ellis's letter (13 September, p. 655), still alive after more than 20 years, belongs to this type, and it is interesting to note that the biopsy from the perforated palate shows no evidence of neoplasm.

The Wegener type of disseminated granuloma, originating in the respiratory tract, may be arrested by corticosteroid treatment. Histopathological examination shows giant cellular granulomatous vasculitis. It may remain local, or become systemic, eventually involving kidneys, spleen, lungs, etc. It is important to emphasize the rhinogenous origin of Wegener's granulomatosis.[3] The presenting signs may, of course, be situated elsewhere—for example, larynx, ears, skin; or the systemic manifestations—for example, purpura—might overshadow the apparently trivial nasal discharge and sinusitis during the early stages of the disease.

Granuloma gangrenescens (used as a clinical term) is a malignant neoplasm, such as malignant lymphoma, Hodgkin's disease, anaplastic carcinoma. According to Walton,[4] after a latent period of six to twelve months metastatic lesions develop.

As we have pointed out,[5] cases must be excluded from any aetiological consideration of non-healing granuloma of the nose in which a neoplasm, such as malignant lymphoma, was diagnosed with accuracy. This approach would assist in the diagnosis, treatment, and better understanding of the two main types of non-healing granuloma of the nose and midline facial tissues. In our experience there are two clearly defined histological pictures at either end of a spectrum between the Stewart type and the Wegener type, and when we see the latter clearly defined we feel justified in making the diagnosis of Wegener's granuloma, even in the apparent absence of systemic involvement.

Wegener's granuloma was diagnosed from nasal biopsy 15 years ago in a man then aged 38. Vascular granulations were present in the roof of both nasal vestibules, with progressive spreading to nasal cavities resulting, after four years, in an atrophic condition, septal perforation, and deformity of nasal bridge in lower third. Left episcleritis appeared after 10 years and left 12th nerve palsy after 12. Corticosteroid treatment has been given for the past 14 years. The patient continues to be fully employed as a bus driver. No systemic effects of the condition have been observed to date.

Despite much speculation, the causation of non-healing granuloma remains unknown. The obscurity which surrounds these granulomas can only be penetrated by a study of accumulated cases (Professor D. F. N. Harrison, 27 September, p. 779). The condition comes within the purview of the recently established E.N.T.-Tumour Panel with its diagnostic and follow-up organization based on this institute and sponsored by the British Empire Cancer Campaign for Research.

We wish to thank Mr. B. Cohen, F.R.C.S., for allowing us to use the patient's case report.
—We are, etc.,

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