improvement as demonstrated by reduction or in some cases disappearance of spontaneous pain in walking (so much so that after many years two patients were able to go upstairs without pause).

The rheographic tracing was not modified in one case; in six others it showed an improvement both in baseline conditions and after trinitrin.

More prolonged and extended trial is needed to confirm the preliminary observations.—We are, etc.,

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¹ Calne, D. B., Spiers, A. S. D., Stern, G. M., Laurence, D. R., and Armitage, P., *Lancet*, 1969, 2, 973.

² Calne, D. B., Brennan, J., Spiers, A. S. D., and Stern, G. M., *British Medical Journal*, 1970, 1, 474.

³ Nyboer, J., *Circulation*, 1950, 2, 811.

Cancer, F.D.P., and Radiotherapy

SIR,—Your leading article "Fibrin and Cancer" (11 December, p. 641) is a welcome survey of our knowledge in this field. Owing to the coagulative and fibrinolytic properties of malignant tumours fibrin degradation products (F.D.P.) may occur in the blood in patients with such neoplasms. We recently reported (20 November 1971, p. 458) the finding of F.D.P. in as many as 72% of women with malignant ovarian tumours.

We have since had the opportunity of observing some cases of recurrent malignant tumours of the ovary in which the F.D.P. in the blood disappeared after radiological treatment. An illustrative case is reported below.

A girl born in 1953 was subjected to right-sided salpingoophorectomy in June 1969 because of an ovarian androblastoma of uncertain degree of malignancy. Six months later she was re-admitted to hospital because of a large palpable recurrence. Analysis revealed F.D.P. in a concentration of 100 µg/ml. After radiotherapy alone the abdominal mass was no longer palpable and F.D.P. were no longer demonstrable. In June 1970 a new recurrence was diagnosed and the F.D.P. concentration was found to be 300 µg/ml. After irradiation and surgical excision of all visible malignant tissue the F.D.P. disappeared. No F.D.P. were afterwards demonstrable until August 1971, when a third recurrence was detected. Despite reoperation, radiation, and treatment with cytotoxic drugs the tumour grew rapidly, and the patient died in January 1972. The F.D.P. were then 50 µg/ml.

Thus every recurrence was accompanied by the appearance of F.D.P. in the blood. The first recurrence responded well to radiation alone and the F.D.P. disappeared. The symptoms and the F.D.P. disappeared also after surgical and radiological treatment of the second recurrence. The third recurrence was fatal.

It has recently been shown in organ culture studies that the fibrinolytic activity of tumours varies with their vascularity.¹ Irradiation of tumours damages their vessels,² probably with inactivation of the endothelial cells that synthesize the fibrinolytic enzyme. If so, this would explain the disappearance of F.D.P.

We have also regularly found that the

F.D.P. temporarily increases about three to four weeks after the beginning of irradiation of ovarian carcinoma. This increase might be explained by degeneration of the tumour by the radiation with entry of thromboplastic substances into the bloodstream.—We are, etc.,

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¹ Björlin, G., Pandolfi, M., and Astedt, B., *Experientia*, in press.

² Errera, M., and Forssberg, A. G., *Mechanisms in Radiobiology*, vol. 2, p. 153. New York, Academic Press, 1960.

Intravenous Glucagon

SIR,—Dr. J. R. Condon and others (5 February, p. 376) say that the only alternative drug to glucagon acting over a short period in Paget's disease is mithramycin. We have noted similar effects with actinomycin D on RNA inhibition¹ in the same journal on the next page to that of Dr. Condon and colleagues' article about mithramycin.²

We have now shown in subsequent studies³ that the effects of these two agents are quite similar. In addition, we find that relief of symptoms can be maintained by weekly dosage of mithramycin or actinomycin D at dosage which does not cause marrow depression or hepatocellular drainage.—I am, etc.,

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¹ Fennelly, J. J., and Groarke, J. F., *British Medical Journal*, 1971, 1, 423.

² Condon, J. R., et al., *British Medical Journal*, 1971, 1, 421.

³ Fennelly, J. J., *Irish Journal of Medical Service*, 1971, 140, 431.

Halo Naevus—a Frustrated Malignant Melanoma?

SIR,—The same antibodies thought to be specific against the cytoplasm of malignant melanoma have been discovered circulating in all nine patients with a halo naevus. This is a pigmented mole that becomes surrounded by a circular area of depigmented skin during its spontaneous resolution. We postulate that these naevi, always considered benign, may represent the successful rejection phase of malignant melanoma. It is known that rarely melanomas do resolve, sometimes accompanied by halo formation.

During the halo naevus phase of its spontaneous remission a pigmented mole becomes invaded by a massive infiltrate of lymphocytes—signs usually taken to indicate an immune response. This self-healing melanocytic naevus has long been the subject of speculation concerning its pathogenesis and significance.^{1,2}

Recent immunological studies^{3,4} in patients with malignant melanoma have shown the presence of humoral antibodies directed against the plasma membrane and the cytoplasm of the tumour. The cytoplasmic antigen is common to all malignant melanomas: its corresponding antibody is found in early localized malignant melanoma and cross-reacts with the tumour cells of other melanoma patients. It was decided therefore to exploit this situation of a common cross-reacting cytoplasmic antigen to study sera from patients with a variety of skin tumours and pigmented naevi. Sera (diluted 1 in 4) from patients were tested for antibodies by the indirect immunofluorescent technique, incorporating a number of refinements.⁵ The

FIG 1. Clinical photograph (ultraviolet) of halo naevus on back.

fluorescence was read as positive only if over 25% of the malignant melanoma cells on the smear had positive cytoplasmic staining.

Humoral antibody directed against the cytoplasm of malignant melanoma was traced in all the patients tested with malignant melanoma without metastases (54 primary or localized lesions); and in nine patients with halo naevus, three solitary and six multiple. The patients ages were: 8, 9, 12, 13, 13, 14, 17, 28, and 35 years. The small boy aged 9 years had had a solitary halo naevus on his cheek associated with a high titre of cytoplasmic antibodies. When his serum was retested six months after the lesion had been surgically removed no antibodies could be detected.

Cytoplasmic antibody to malignant melanoma cells was not found in patients with halo naevus (multiple lesions) that had resolved some years previously and had re-pigmented spontaneously; or in six with multiple melanocytic naevi (including two children with acutely erupting lesions and one man with scores of moles that had become acutely inflamed after dithranol treatment for his psoriasis); or in 46 with vitiligo (unassociated with halo naevi); or in four with "benign juvenile melanomas." Negative results were also found in 39 patients who had been referred with the diagnosis of malignant melanoma and who proved to have other conditions.

FIG 2. Positive cytoplasmic staining (patient's serum: F.I.T.C.-labelled IgG) of a malignant melanoma cell (smear preparation x 600).

We applied stringent criteria to detect circulating cytoplasmic antibody before recording a patient's serum as positive. All the

54 patients with localized or primary malignant melanoma had circulating cytoplasmic antibody. A few patients formerly positive but who had converted to negative, and some who on clinical grounds had a primary lesion but who had negative tests for cytoplasmic antibody, were found to have developed metastatic lesions.

It is postulated that the halo naevus represents a seldom seen interim stage natural protective mechanism—that is, a rejection phenomenon of malignant melanoma. It is the visualization, so to speak, of the surveillance system normally so effective in preventing malignant melanoma from developing in every individual. The study of such aspects in the behaviour of moles and melanomas raises the question not only why are halo naevi spontaneously rejected and heal, but why do malignant melanomas develop and persist in patients who in all other respects appear to have normal and intact immunological mechanisms.—We are, etc.,

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- 1 Rolleston, H. D., *Proceedings of the Royal Society of Medicine*, 1910, (Clinical Section), 3, 195.
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Particles in Spleens

SIR,—Dr. A. E. Stuart and others have described unusual particles in spleens from cases of idiopathic thrombocytopenic purpura (I.T.P.) and hemolytic anemia (18 December 1971, p. 721). They have called our attention to morphological similarities of these particles with platelet lysosomes, yet they have interpreted these structures as "virus-like particles."

We have observed similar structures in the spleen from a case of sickle cell disease¹ as well as in spleens from other haematological disorders. These structures are most often seen in spleens where phagocytic activity in the spleen is exaggerated (I.T.P. and various haemolytic anemias). They tend to occur in clusters, particularly in sinusoidal linings cells and occasionally in adventitial cells and other macrophages. On morphological grounds we believe they represent platelet lysosomes. The interaction of platelet and vascular endothelium is well known.^{2,3} Platelets are often seen within the vascular endothelium. Recently Molnar and Rappaport⁴ have described the presence of ferritin-laden platelets in sinusoidal lining cells of the spleen in cases of hereditary spherocytosis. Since the lining cells, though phagocytic, notoriously lack lysosomal structures, these workers have suggested that platelet lysosomes may play a part in digestion of red cell particles within the sinusoidal endothelium. It is likely that the phagocytic function of splenic sinus endothelium is accomplished through collaboration of these reticular cells and platelets: the lining cells take up both particulate matter of various origin and platelets, then they use platelet

lysosomes to digest particles they have taken up.

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- 1 Tavassoli, M., and Weiss, L., in *Formation and Destruction of Blood Cells*, ed. T. J. Greenwalt, and G. A. Jamieson, Philadelphia, Lippincott, 1970.
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- 4 Molnar, Z., and Rappaport, H., *Blood*, 1972, 39, 81.

Testing for Australia Antigen

SIR,—Mr. J. M. Leach and Mr. B. J. Ruck (4 December, p. 597) describe a latex agglutination test for the detection of Australia antigen (HAA) which seems to be quite promising. One problem, however, is a large number of false positives occurring in fresh serum and I think this can readily be eliminated by heat inactivation at 56°C for 30 minutes. The heat would readily destroy complement factor, which has caused false positive latex fixation tests for rheumatoid factor, and we have recently found that a complement factor-like substance can inhibit the detection of Australia antigen when using reaction electrophoresis.¹ This is logical since complement factor mimics rheumatoid factor, which is capable of masking the presence of Australia antigen—even the ultracentrifuged Australia antigen has been shown to be an antigen-antibody complex.^{2,3}

The heat inactivation of the sera to be studied by latex fixation testing would eliminate some false positives (a serum containing true rheumatoid factor might well give a false positive reaction) and also uncover "masked" Australia antigen in certain specimens—thus both specificity and sensitivity would be enhanced.—I am, etc.,

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- 1 Ziegenfuss, J. F., Miller, J., Rossman, D., *New England Journal of Medicine*, 1971, 284, 1104.
- 2 Cheng, C. T., Persellin, R. H., *Annals of Internal Medicine*, 1971, 75, 683.
- 3 Blumberg, B. S., Millman, I., Sutnick, A. I., and London, W. T., *Journal of Experimental Medicine*, 1971, 134, 3205.

Donors for Organ Grafting

SIR,—We read with considerable interest your leading article (4 March, p. 582) urging the need for more potential organ donors for transplants. A paper will appear shortly,¹ in which we have suggested that the condition of "irreversible brain damage" be legally certifiable by two doctors; they should be independent of the transplant team and one should be nominated by the relatives if they so wished. At the moment, there could be circumstances in which the doctor stopping the resuscitation measures before organ excision might be acting illegally technically.

One would leave the traditional certification of death as it is at present, thus avoiding future legal problems associated with decisions about the precise moment of death. We believe that, with suitable safeguards, the new certification of "irreversible brain damage" should be required before

organ excision is started. This certification would act as legal authorization to stop resuscitation, and to proceed with excision. It would give to transplant surgeons legal protection which may be lacking at present. With this certification, relatives would probably be as willing to authorize excision as they are in the United States.² One would hope that it would go some way towards allaying public anxiety of premature organ excision, and it should thus increase the number of potential organ donors.—We are, etc.,

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- 1 Hillman, H., and Aldridge, T. M., *Solicitors Journal*, in press.
- 2 Griep, R. B., Stinson, E. B., Clark, D. A., Dong, E., and Shumway, N. E., *Surgery, Gynaecology, and Obstetrics*, 1971, 133, 792.

Thrombosed Shunts

SIR,—It is well known that when an external arteriovenous shunt is thrombosed and removal of the thrombi fails revision of the shunt is necessary. In patients in whom this has happened repeatedly it can be a great problem to find vessels in good condition for a revision. Two methods are described for salvaging shunts which have thrombosed and which conventional methods have failed to clear.

For external shunts the thrombus was removed through an incision in the vessel distal to the Teflon tip. Angiograms were performed to establish the extent of the thrombosis. Under local anaesthesia, a 2-cm transverse skin incision was made over the site of the thrombosed vessel. A sphygmomanometer cuff was inflated to prevent embolization of the thrombus and to facilitate the phlebotomy. The thrombus discharged itself spontaneously through the incision, aided by irrigation with heparinized saline through the silastic tube of the shunt. To clear thrombi from the arterial side a similar technique is used, the vessel being occluded by a bulldog clamp proximal to the arteriotomy. A rather unusual case prompted me to employ open thrombectomy when a dislodged Teflon tip was removed via a transverse phlebotomy, and the shunt remained patent for a further three months, at which time the patient had a successful cadaveric renal transplant.

Thrombosed internal fistulae can be refashioned by end-to-end anastomosis of the vessels proximal to the block. Under local anaesthetic a transverse skin incision is made 3-4 cm proximal to the previous thrombosed fistula. The artery is formed into a loop, leaving the vein in a straight line.

The above methods have been successful so far in all cases.—I am, etc.,

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Traumatic Perforation of Oesophagus

SIR,—Your timely leading article (26 February, p. 524) concluded with the following sentences: "It is encouraging that the in-