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