Treatment of Choriocarcinoma with Cytotoxic Drugs

SIR,—I read the article (August 6, p. 426) on treatment of six cases of choriocarcinoma by a combination of methotrexate and 6-mercapto-purine with interest. Without wishing to detract in any way from the courageous attack on this very lethal tumour by Drs. K. D. Bagshawe and Janetta M. McDonald, I would like to raise certain points.

Chorionic tumours, even more than other tumours, vary greatly in their degree of inherent malignancy. Different categories are described—e.g., invasive mole, "intrinsic" chorionepithelioma, chorioadenoma destruens, and choriocarcinoma—but, as Willis suggests, there is probably a continuous gradation in malignancy. The difficulties in histological diagnosis are well known, and even perfectly benign moles may exhibit deep invasion of the uterine muscle and invasion of veins. The gonadotrophin titre, also, may persist at a raised level several months after expulsion of a mole, whose behaviour in other respects appears quite benign.[1] There are occasional reports of regression of metastases after treatment of the primary lesion alone,[2] and my gynaecologist colleagues have told me of such cases in their own practice. A case that I treated over two years ago may be of interest.

A woman of 20 had a miscarriage in December, 1957, in the third month of pregnancy, due to hydatidiform mole. In January, 1958, the Hogben test for gonadotrophic hormone was positive at a dilution of 1 in 300. She was allowed to go home, but soon afterwards she was readmitted with a history of abdominal pain and small haemoptyses. On March 3, 1958, exploratory laparotomy showed infiltration of the broad ligaments and pelvic mesocolon by numerous haemorrhagic deposits. There was a large purplish mass beneath the peritoneum on the posterior abdominal wall, at the level of the sacrum. A portion of this taken for section showed clot with syncytial tissue. It was regarded as choriocarcinoma. *X*-ray of chest showed several rounded opacities in both lung fields. Films taken at intervals of a week or two showed these to be increasing in size.

It was decided to start treatment by *x*-irradiation of the lower abdomen and pelvis, in the first place. I was prepared to go on and treat the chest metastases by thoracic *x*-ray "bath" technique, if necessary. Treatment was commenced on March 24, 1958, by a single large anterior field, 15 by 20 cm. (Technical factors: 250 KV, HVL 1.5 mm. Cu; 50 cm. FSD). At this time the patient's condition was rapidly deteriorating. She was losing bright blood P.V., there was diffuse rigidity of the lower abdomen, and some fixed flexion of the left hip due to spasm of the ilio-psoas muscle (invaded by tumour deposits), and she was coughing up small quantities of blood. The course of treatment was completed on April 16, a dose of 2,500 r being delivered to anterior and posterior fields, the through and through tumour dose being of roughly the same order.

During and following treatment the uterine bleeding diminished, became brown, and finally ceased. The abdominal rigidity and spasm of ilio-psoas gradually passed off. *X*-ray of chest on the last day of treatment showed disappearance of some opacities, and shrinkage of others. By May, 1958, the patient was up and walking about normally, there were no abnormal signs in pelvis or abdomen, and *x*-rays showed further shrinkage of pulmonary opacities. Aschheim–Zondek test was negative in dilutions of 1/10 to 1/50.

The patient has remained well since apart from occasional fits (she has been subject to epileptic seizures since the age of 15). *X*-rays of chest showed disappearance of all metastases, except for one small shadow at left apex still *visible* as late as April, 1959. By January, 1960, *x*-ray of chest was completely clear. When last seen (in July, 1960) she was in excellent health.

There can be no question that this patient had a highly malignant choriocarcinoma. Treatment directed to the primary tumour (the uterus was not removed) and pelvic metastases was followed quickly by regression of all signs of disease in the treated area. The pulmonary deposits also diminished concurrently, but took longer to clear altogether; these could not have been influenced *directly* by the abdomino-pelvic irradiation.

What can one conclude from this experience? Choriocarcinoma of the uterus is reputed to be an extremely radio-sensitive tumour. (Oddly enough, it is hardly mentioned in the four main standard textbooks of radiotherapy published in England, and I have not had opportunity to search the literature.) Sceptics may argue that regression would have taken place spontaneously in this case, but the concurrence with radiotherapy would seem a remarkable coincidence.

Ablation of the primary tumour and the ovaries (whether by surgery or irradiation) seems to be followed in some cases by regression of metastases—as though these had not a completely autonomous viability, but were perhaps, in some sense, "hormone-dependent." Of the six cases reported, hysterectomy and oophorectomy was performed in three out of five cases who survived. Credit for control of the disease in the remaining two cases can only be given to the cytotoxic drugs—and most convincingly in Case 5.

I hope the authors will not take this comment as grudging or hypercritical of their therapeutic efforts. But I would make a plea that the potential value of radiotherapy should not be overlooked in this desperate condition, in which the dangers and discomforts of drug treatment are clearly considerable.—I am, etc.,

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REFERENCES

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2 Lackner, J. E., and Leventhal, M. L., *J. Amer. med. Ass.*, 1932, **98**, 1136.

Meigs's Syndrome

SIR,—Dr. Peter A. Emerson (August 6, p. 467) once again suggests that a pleuro-peritoneal opening is responsible for the hydrothorax in Meigs's syndrome. He ignores clinical evidence: for aspiration of the hydrothorax may lead to complete disappearance of the pleural effusion, even though in the same case the ascites recurs despite repeated tappings. This was a striking feature in Lawson Tait's case,[1] the first to be treated successfully by ovariotomy, and in a case recently reported by me.[2] Nor is the suggestion of a one-way valve-like communication between the two cavities acceptable. Cowan and his colleagues,[3] using radioactive colloidal gold (^{198}Au), have demonstrated the existence of a pathway from pleural to peritoneal cavity as well as in the opposite direction. The percentage dosage of isotope delivered to the opposite cavity excluded the possibility of a direct communication, since the amount transported was not proportional to the volume of fluid in each cavity. Dr. E. W. Emery and I have recently confirmed this experiment, using a different tracer. Furthermore, simultaneous estimation of the concentration of the tracer in the bloodstream does not point to this route as a likely means of transfer. Some form of rapid lymphatic transport across the diaphragm is therefore the only possible route; it is