Public Health Service, 1956) shows much higher rates for cardiovascular deaths at all ages for the single, widowed, and divorced males than for the married. The differences are even more pronounced for the non-white population. Among females the widowed and divorced show a similar excess mortality from these causes; single coloured women also show a very marked excess. Single white women, both in the United States and in Britain, show no excess cardiovascular mortality.

This favourable mortality experience of the married is not confined to the cardiovascular group of diseases, however; similar results are found for such diverse conditions as pneumonia, peptic ulcer, and cirrhosis of the liver. There are many mechanisms which may account for such findings, and it is impossible to determine to what extent they are due to a beneficial influence on health of married life; to the deprivations and worries of the single, widowed, and divorced; or to the health selection which occurs at marriage.

We have, fortunately, too few deaths in this follow-up study to be able to relate our blood-pressure readings to mortality rates or expectation of life, and too few widowed and divorced to warrant their separate analysis until further material is available.

Conclusions and Summary

The results of the first follow-up survey of arterial pressure in the population of one of the Welsh mining valleys are reported. The original measurements were made in 1954 on a random sample of this population and all first-degree relatives living within 25 miles. Repeat readings were made four years later, at the same time of year, in 1958. The recordings were all taken by one observer, under identical circumstances, without reference to previous readings.

The results suggest the possibility that arterial pressure, when full allowance is made for age, may be increasing in middle-aged males. This trend is occurring to a greater extent in men previously engaged in heavy jobs, though they still have lower pressures than those previously in light occupations. These findings are discussed in terms of the secular trend in mortality from cardiovascular diseases reported by the Registrar-General.

Blood-pressure was again found to correlate with family size, and increases in pressure were less in those subjects who had children during the four-year interval. The differences in the rate of increase of pressure with age between those having children and those not having them appeared sufficient to explain the marked difference found previously between childless men and women and those with large families.

In women, those adding salt at table to cooked meals, who presumably have a larger salt appetite, were found to have lower blood-pressures and smaller pulse-pressures in 1958, to have gained less in blood-pressure and pulse-pressure during the previous four years, and to be lighter than women who do not take additional salt in this way. No comparable differences were found in the men.

I should like to record my thanks to the people of the Rhondda Fach, who have again so willingly co-operated in this survey; to my colleagues at the Pneumoconiosis Research Unit, in particular Dr. J. C. Gilson, the Director, and Dr. A. L. Cochrane and Mr. P. D. Oldham for valuable discussion and advice; to Dr. T. G. Morris for the analyses of sodium output; to Miss G. Jones and all members of the field survey team who helped with the collection and analysis of the material, and especially Miss L. Roberts, who provided secretarial help, and Mr. F. Moore, who assisted with all the field work.

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METHOTREXATE IN TREATMENT OF METASTASIZING CHORIONCARCINOMA

A CASE REPORT

BY

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The known predilection of chorioncarcinoma to penetrate blood vessels and metastasize early makes it obvious that treatment must be immediate if it is to be successful. Once metastases have appeared they may be treated as they are found, but the long-term results in proved cases of chorioncarcinoma are disappointing.

Reports on the treatment of these advanced cases with folic acid antagonists and 6-mercaptopurine have come from America, but so far there has been no comparable group of cases reported from this country. The case detailed below, though ultimately fatal, is reported in the hope that interest may be aroused in this form of therapy, which may be of value in certain of these advanced cases.

Dosage of Methotrexate in Chorioncarcinoma.—Hertz *et al.* (1958) recommended a dosage of 1–4.5 mg. per kg. body weight for the first course of treatment, to be followed by subsequent courses in which a dose of 2.5 mg. per kg. body weight was employed. The calculated amount of methotrexate was given, either orally or by the intravenous route, in divided doses daily over each five-day course. This dosage is in excess of

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the amounts normally given in the treatment of acute leukaemia, in which condition the drug has been employed with some success. The oral route of administration is preferable.

Toxic Effects of Methotrexate.—In the cases reported by Hertz *et al.* (1958), reversible toxic effects encountered during treatment included stomatitis, glossitis, pharyngitis, marrow depression, petechiae, anorexia, emesis, proctitis, and diarrhoea, the pattern varying from patient to patient. With the exception of marrow depression, all the above toxic effects were encountered in the case here reported; severe melaena was a further complication in this patient.

Investigations Made Before and During Therapy.—These were listed by Hertz *et al.* (1958), the patient being weighed in order to calculate methotrexate dosage, the daily urinary gonadotrophin output estimated, marrow biopsy performed, a full blood count made, and the blood urea estimated. During the course of treatment daily estimations of the body weight, fluid intake and output, urinary gonadotrophin excretion, haemoglobin level, white-cell count, reticulocyte count, platelet count, and blood urea were made and weekly assessment of palpable metastases was performed. In addition, serial chest *x*-ray films were taken.

As methotrexate is excreted largely in the urine, an adequate fluid intake is essential, and hepatic or renal dysfunction would be a contraindication to the intensive therapy outlined. Maximum toxic effects are encountered four to five days after the completion of a course of the treatment and are not controlled by withdrawal of the drug. Further courses of treatment are therefore not started until all toxic effects have disappeared.

Case Report

A married woman aged 35 was admitted to hospital on November 29, 1958, with vaginal haemorrhage following a normal confinement at home 19 days previously. The uterus was bulky, and retained products of conception were obtained at curettage. The microscopical report showed organizing blood-clot with fragments of degenerating chorionic villi and trophoblastic tissue. She was discharged, free of bleeding, four days later, but was readmitted on December 31 with further vaginal bleeding. Examination under anaesthesia revealed the uterus to be bulky, and further retained products were obtained from curettage. Microscopical examination showed degenerate products of conception present, there being some patchy polymorphonuclear infiltration of the tissue.

The patient was discharged, free of bleeding, 10 days later and was not seen again until she attended the outpatient department on February 16, 1959. She stated at this time that bleeding had recurred some two weeks after she had left hospital, but that she had not sought medical advice again until the present attendance.

On examination she was febrile, looked ill, and had lost weight. Abdominal examination revealed a mass present in the hypogastric region, equivalent in height to a 14-weeks pregnancy. The origin of this mass was felt to be uterine, and this was confirmed on bimanual palpation, both tubes and ovaries being involved in the mass. Speculum examination showed the cervix to be normal, but there was a reddish-blue, haemorrhagic, polypoidal mass present involving the right lateral fornix of the vagina and measuring 4 cm. in diameter (Fig. 1). A diagnosis of chorioncarcinoma with metastatic spread was made, and the patient was admitted for further investigation and treatment.

Investigations.—Chest *x*-ray examination (Fig. 2) revealed a rounded opacity in the right mid-zone and a second opacity at the right base, the appearance being that of metastases. Blood count: haemoglobin, 11 g./100 ml.; white cells, 11,000/c.mm. Hogben test: positive neat and in dilution.

Examination under anaesthesia on the day after admission confirmed the previous findings. A biopsy of the mass in the vaginal wall showed blood-clot with large hyperchromatic trophoblastic tissue cells with large bizarre nuclei. The appearances were those of a chorioncarcinoma involving the vaginal wall.

In view of the widespread metastases, it was decided that the patient should be treated with "methotrexate" (4-amino-N^{10}-methyl-pteroylglutamic acid) after preliminary haematological investigation.

Progress

Methotrexate therapy was begun on February 23, and this and subsequent courses of treatment are shown in

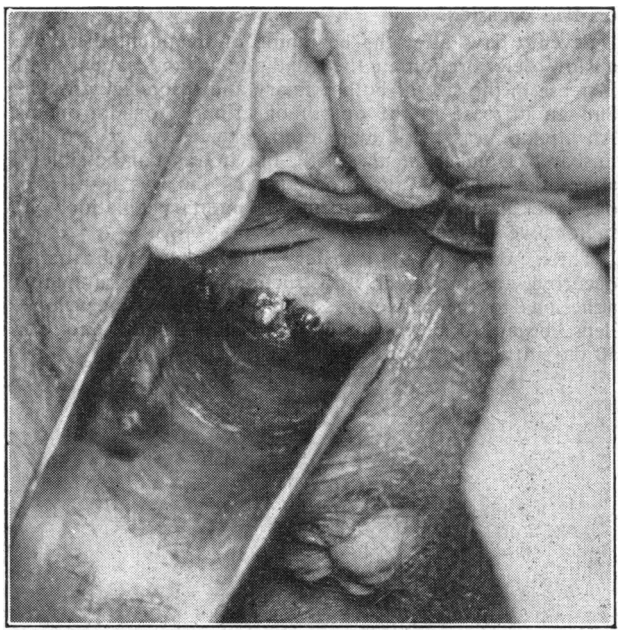

FIG. 1.—Appearance of vaginal metastasis before methotrexate and 6-mercaptopurine therapy.

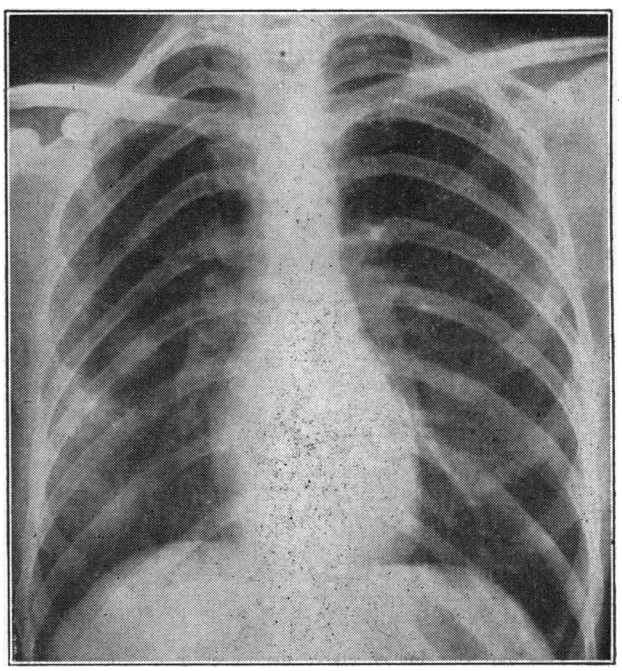

FIG. 2.—Chest *x*-ray film before beginning of treatment.

Fig. 3. 24 days after treatment had started there was a diminution in the size of the tumour mass in the pelvis and of the vaginal metastasis. Chest *x*-ray examination revealed more metastases present (Figs. 4 and 5), though there had been no increase in size of the ones present in the earlier films. 38 days after the beginning of treatment there was an increase in the size of the tumour mass. In addition to methotrexate, 6-mercaptopurine was given in a dosage of 300 mg. daily for the five days of the course and continued thereafter as a daily dose of 100 mg. This dosage of 6-mercaptopurine is greatly in excess of the dosage normally employed when the drug is used for the treatment of acute leukaemia.

Shortly after this combined therapy was begun there was almost complete regression of the vaginal metastasis (Fig. 6), considerable diminution in the size of the abdomino-pelvic mass, and marked suppression of the urinary gonadotrophin output, the latter being completely negative on two occasions.

Seventy days after the beginning of treatment there was a slow deterioration in the condition of the patient, with increase in the size of both primary and secondary growths, and an increase in the output of urinary gonadotrophins. An attempt was made to immunize her to the cells of her husband (Doniach *et al.*, 1958), but it was not possible to assess the value of this procedure, as she was transferred one week later for assessment for pituitary ablation with radioactive yttrium.

Three days after transfer, small-bowel obstruction occurred, and though this obstruction, due to inflammatory adhesions to the pelvic mass, was relieved, she developed ileus, began to bleed heavily from the vagina, and died 10 days after operation.

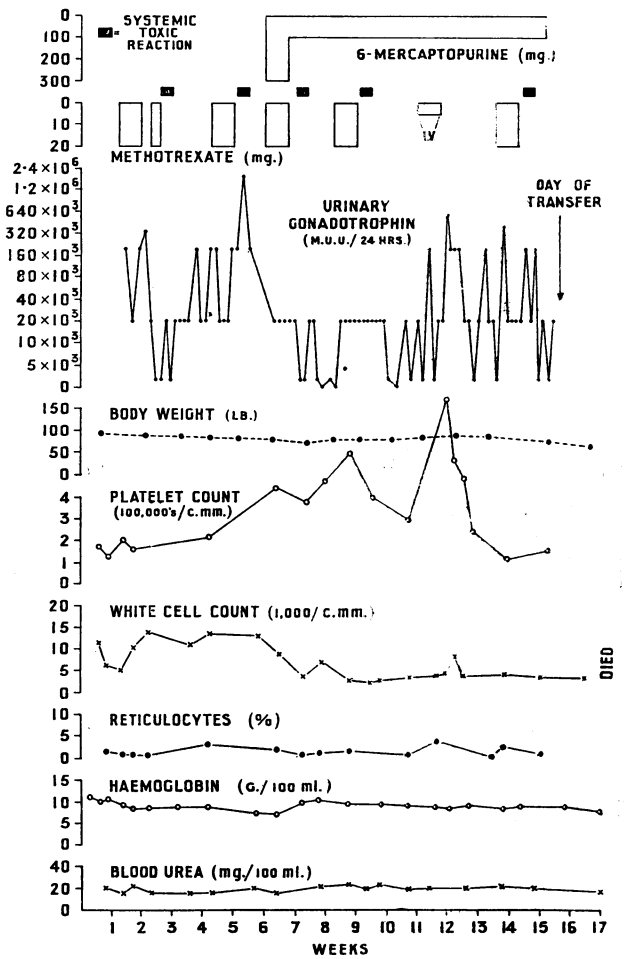

FIG. 3.—Chart showing effects of methotrexate and 6-mercaptopurine therapy.

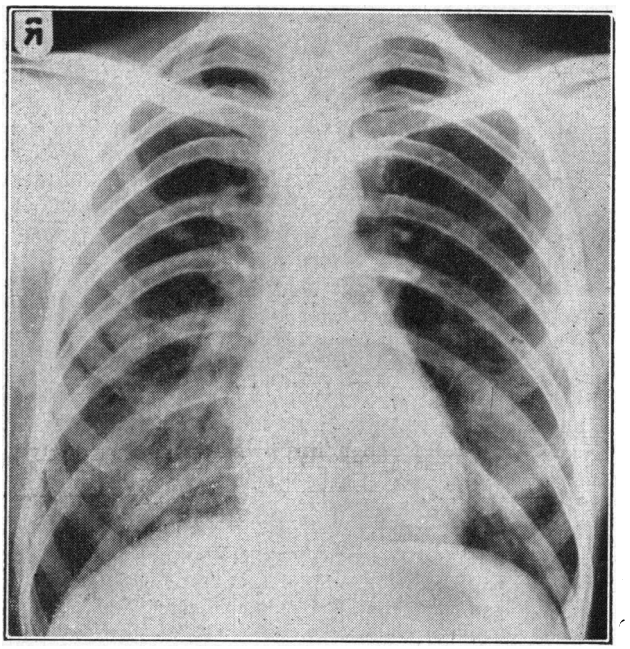

FIG. 4.—Chest *x*-ray film after three weeks' treatment.

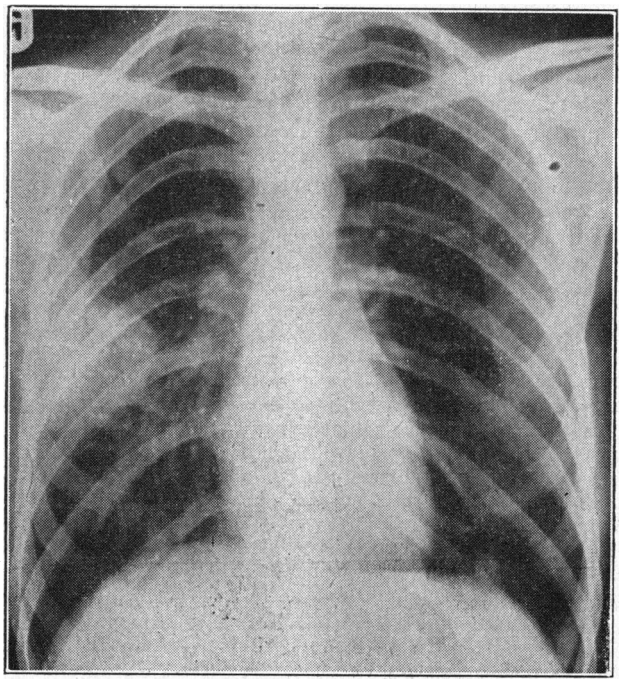

FIG. 5.—Chest *x*-ray film four weeks before death, showing marked increase in size of pulmonary metastases.

At necropsy the uterus, uterine tubes, and ovaries were involved in the mass of neoplastic tissue, the vagina also being invaded. Both lungs contained multiple metastases, one of which had begun to invade the chest wall. Microscopy confirmed that the metastases were chorioncarcinoma.

No further urinary gonadotrophin estimations were made during this period immediately preceding death.

Discussion

Folic acid is known to be essential for the growth of the female genital tract and for normal embryonic development. Hertz and Sebrell (1944), Hertz (1948a, 1948b), and Hertz and Tullner (1949) demonstrated the inhibition of oestrogen-induced growth in the chick

oviduct and monkey uterus in animals maintained on a folic-acid-deficient diet or treated with antagonists of either folic acid or adenine. The mode of action of the folic-acid antagonists is as an antimetabolite to folic acid, probably by inhibiting the conversion of folic acid to folinic acid, whereas 6-mercaptopurine is an antimetabolite of adenine and hypoxanthine and acts on cell nuclei.

It was therefore postulated that chorioncarcinoma and related trophoblastic tumours, originating in foetal chorion and initially involving the uterus, might prove responsive to treatment with the folic-acid antagonists. Initial experience in the treatment of such tumours with the folic-acid antagonist methotrexate was then reported

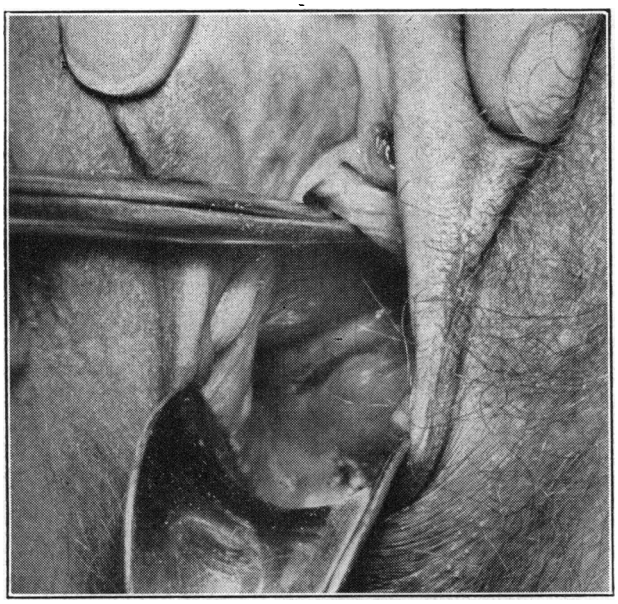

FIG. 6.—Disappearance of vaginal metastasis following treatment.

(Li *et al.*, 1956, 1958). The latter authors state that treatment with methotrexate and 6-mercaptopurine produced a response in females with these tumours, but that there was no response in the case of such tumours occurring in the male, even if oestrogen was administered at the same time. It was postulated that in the female the growth arose from the foetus and was therefore homologous with, but not arising from, maternal tissue, whereas in the male the tumour in the testis was truly autogenous, and that this might explain the difference in response to therapy.

Hertz *et al.* (1958) discussed the results of treatment with methotrexate of 27 patients who presented unequivocal radiological, hormonal, or clinical evidence of metastatic trophoblastic tissue. They stated that such tumours present a unique quantitative biological indicator of their extent and progression in terms of the patient's urinary excretion of chorionic gonadotrophic hormone and that the latter hormonal titre (measured in mouse uterine units per 24 hours) may be used as a guide in the clinical evaluation and response to therapy. It was also noted that a value of 200 mouse uterine units or less, per 24 hours, was normal, as this figure was found in patients not suffering from chorioncarcinoma or related trophoblastic tumours who had previously undergone bilateral oophorectomy.

Of the 27 cases described, remissions varying from 29 to 2 months were obtained in all but one patient who had received more than one course of therapy. In five patients continuing remissions had been attended by no radiological, physical, or hormonal evidence of residual disease; in 11 patients with initial remission, variable methotrexate resistance had been encountered with varying manifestations of residual disease; 6 patients with initial response had developed resistance to methotrexate and died; one patient died of drug toxicity during remission, and drug toxicity was felt to have contributed to the death of two other severely debilitated patients.

The reported case therefore falls into the third group described by Hertz *et al.* (1958)—namely, that there was initial response to therapy, followed by resistance to methotrexate and death. It was not possible to assess the effects of the attempt which was made to immunize the patient to her husband's cells, and it was unfortunate that the general condition of the patient was such as to render pituitary ablation impossible. It was felt that the latter procedure might effect some improvement in a condition in which hormone dependency may play a part in the natural history of the disease.

No attempt has been made to draw any conclusions from the case described, which has been reported in order to draw attention to this form of therapy. Difficulty in the collection of a sufficient number of patients suffering from the advanced form of this uncommon disease is obvious, but it is suggested that here, as in America, this form of treatment should be tried. The effect of pituitary ablation in those cases which become resistant to therapy with methotrexate and 6-mercaptopurine is not known, but this method may be of value.

Summary

The effect of methotrexate and 6-mercaptopurine therapy on a patient with metastasizing chorioncarcinoma is described. A plea is made for collection of such cases and for a larger trial of this form of treatment.

I thank Mr. Alistair Gunn and Mr. W. P. Greening for their permission to publish the case; Dr. E. N. Allott for his advice and help in management; and Dr. H. Schwabacher for the serial gonadotrophin estimations. The intravenous methotrexate was supplied from America by Messrs. Lederle.

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Over £1m. is to be spent on new building projects in the next three years, the National Spastics Society was told at its annual meeting in London on October 3. Mr. I. D. DAWSON SHEPHERD, the chairman of the society, said that the programme included a grammar school for spastic children (£180.000), a school for the educationally subnormal (£150.000), and a centre for ineducable children (£170.000) which he described as "the first of its kind in the world."