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METHOTREXATE THERAPY IN TWO CASES OF TROPHOBLASTIC TUMOURS OF THE UTERUS INVOLVING THE LUNGS

by

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Malignant tumours, like certain bacterial strains, contain a high concentration of folic acid in comparison with the amount present in normal tissue (BOYLAND); tumour growth has proved to be dependent on the folic acid level, probably due to the unusually lively growth tendency of these tissues and the correspondingly rapid DNA synthesis. A concomitant heightened metabolism of the nucleic-acid precursors of lower molecular weight occurs and this in turn entails a high rate of metabolism on the one-carbon level where folic acid and interrelated reduction forms play an important role.

LI et coll. (1956), HERTZ et coll. (1958, 1961), HRESCHYSHYN et coll. (1961), HAMILTON (1962), CHAN (1962), and others obtained good results with methotrexate in the management of trophoblastic tumours but irreversible toxic effects were also noted. The present authors have aimed at intensifying the diagnostic possibilities with a view to throwing as much light as possible on the nature and extent of the tumour, and then with the aid of microbiologic assays to work out a therapeutic dose that will not lead to irreversible bone

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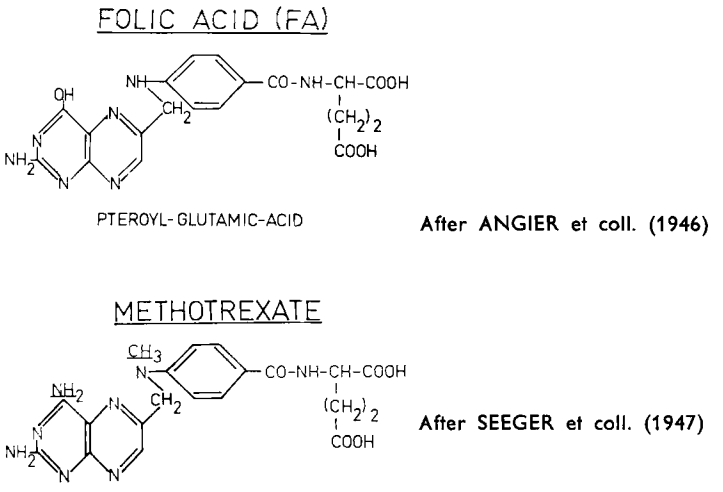


Fig. 1. Structural relationship between methotrexate (4-amino-N^{10}-methyl-folic acid) and folic acid (pteroyl-glutamic-acid).

marrow damage. The fact that these tumours are greatly dependent on a high folic acid content ought in theory to imply a relatively wide therapeutic range.

The chemical structure of folic acid was elucidated in 1946 by ANGIER et coll. on the basis of clinical studies which had shown that liver extract, yeast, and green leaves contain a vitamin, belonging to the B complex, which is necessary for preventing anaemic conditions, especially those of megaloblastic type, in pregnancy and sprue. The possibility that folic acid might play some part in causing malignant growth began to receive attention after its importance for the maintenance of normal haematopoiesis had been demonstrated.

When the chemical structure of folic acid had been cleared up it became possible to synthesize analogues with antimetabolite activity. Aminopterin, or 4-amino folic acid, was found by FARBER et coll. (1948) to be capable of bringing about remissions in children with leukaemia, and SEEGAR, SMITH & HULTQUIST (1947) synthesized a methylated analogue of aminopterin, 4-amino-N^{10}-methyl folic acid, or methotrexate, which proved to be a folic acid antagonist of high potency producing less severe side-effects. LI, HERTZ & SPENCER (1956) found that treatment with methotrexate led to regression of the growth in patients with malignant trophoblastic tumours.

The biochemical activity of folic acid results from FA (folic acid) being reduced to tetrahydrofolic acid (FAH_4), which is a two-step reaction, FA—FAH_2 (dihydrofolic acid)—FAH_4, in which the second step in particular

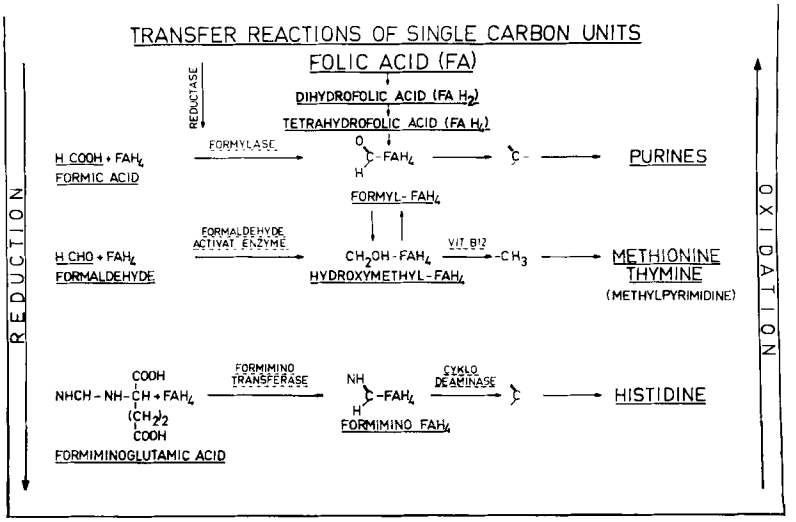


Fig. 2. Transfer reactions of one-carbon units. *1* and *2*. The first two reactions show the possibility of the participation of FA and its immediate derivatives in the synthesis of purines and pyrimidines. *3*. The third reaction is concerned with the FIGlu test and illustrates the forward reaction that is used in its reversible form on histidine loading.

requires the presence of a coenzyme, or folic acid reductase (Rabinowitz 1960, Jukes & Broquist 1961, Boyland 1962). Methotrexate has a greater affinity (x 10^5) for folic acid reductase than FA, and it thus prevents folic acid from reaching its biochemically active form (Werkheiser 1961).

The biochemical activity of tetrahydrofolic acid sets in on the one-carbon level, in the interconversion and biosynthesis of certain amino acids and in the biosynthesis of the purine ring. It also occupies a key position in the synthesis of the DNA pyrimidine, thymine, in which in addition to the activity on the one-carbon level (methylation) it acts as H donor in the thymidylate synthesis (O'Brien 1962). In connection with this, THFA is reduced to DHFA. The thymine synthesis will consequently be quantitatively dependent on the supply of THFA, which in its turn is dependent on the presence of folic acid reductase. In other words, the DNA synthesis will become exclusively sensitive to THFA blocking through the action of methotrexate.

Investigation Methods and Treatment

Repeated determinations to ascertain the folic acid level in serum and whole blood and the serum vitamin B_{12} concentration were carried out before, during and after methotrexate therapy; analyses of sternal marrow, routine examina-

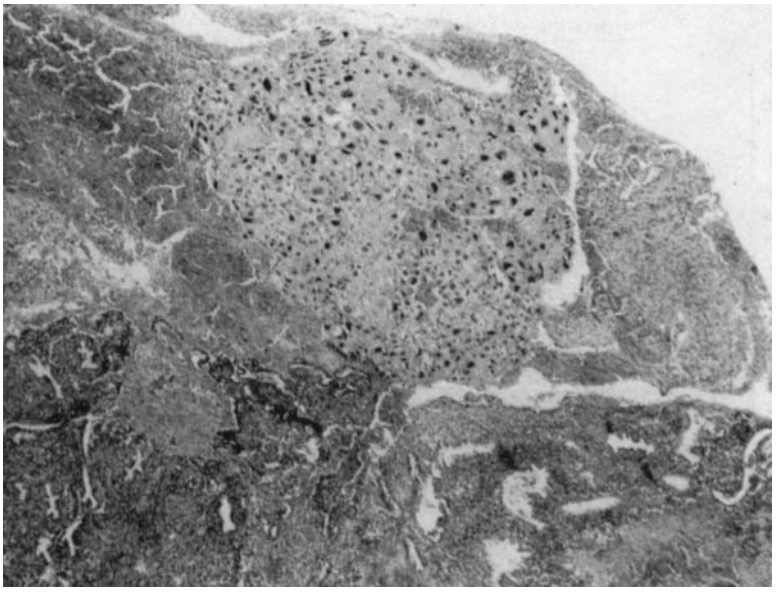


Fig. 3. Case 1. Photomicrograph of biopsy specimen. Chorionic epithelial vegetations with predominance of cytotrophoblasts in a proliferating stage.

tions of the blood, and urinary FIGlu (formiminoglutamic acid) titer determinations after a l-histidine loading, were also made. The plasma histaminase titer was checked repeatedly, and the urinary human chorionic gonadotrophin was measured both quantitatively and, in the case of low values, by qualitative tests for one year after treatment.

The whole-blood folic acid was determined by the method of TOENNIES et coll. (1956) and the serum folic acid by that of BAKER et coll. (1959); both these methods have been described in earlier publications by HANSEN & NYSTRÖM (1961, 1963).

The serum vitamin B_{12} values were determined by a method described by HUTNER et coll. (1956), with a *Euglena gracilis* strain Z.

The formiminoglutamic acid excretion in the urine after histidine loading was ascertained by the method of TABOR & WYNGARDEN (1958); this was done in an endeavour to obtain a biochemical analogy to the antimetabolite effect, in accordance with the principle propounded by NYSTRÖM (1962).

The plasma histaminase determinations were performed by WILLERT (1952), who used AHLMARK's (1944) method. A review of these methods and of their interpretation, as suggested by SWANBERG (1950), may be found in LINDBERG's publication (1963).

Fig. 4. Case 2. Photomicrograph of biopsy specimen. Typical choriocarcinoma with small and large groups of cytotrophoblasts and, around and between these cells, cells of syncytio-trophoblastic type. Abundant infiltration in adjacent muscle tissue.

The quantitative studies of the urinary HCG were carried out at the endocrinologic laboratory at Karolinska Sjukhuset by the DICZFALUSY (1953) method.

Recent developments in immunobiologic assay techniques for HCG (BRODY & CARLSTRÖM 1960, WIDE & GEMZELL 1960, MACKEAN 1960) have made it possible to carry out sensitive qualitative assays when the quantitative concentrations approach zero. Such assays were performed in the present investigation by the method described by WIDE & GEMZELL.

The two cases to be described received methotrexate in three courses at intervals of 2 weeks, each course consisting of 2.5 mg twice a day for 5 days. Hysterectomy and unilateral salpingo-oophorectomy were then performed in both cases. As pulmonary changes resembling metastases persisted after the operation in Case 2, a further two courses were given, one consisting of 2.5 mg three times a day for 3 days, and a further 2.5 mg for one day, and the other of a higher dosage of 5 mg four times a day for 4 days. The cases were kept under observation for one year and showed no signs of the disease.

Both patients had been admitted with a clinical diagnosis of chorionepithelioma and metastatic lesions of the lungs.

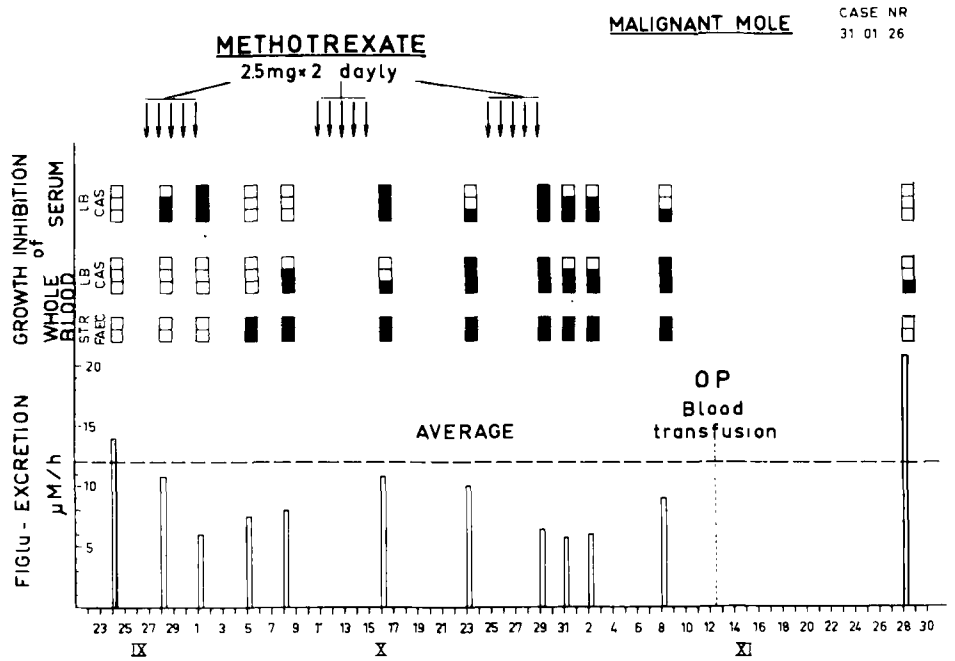


Fig. 5. Case 1. Microbiologic estimations and FIGlu assays. 1. Serum FA. *L. casei* and serum dilutions of 1/20, 1/80 and 1/400 were used. 2. Whole blood FA. *S. faecalis* and *L. casei* were used. For *S. faecalis* two serum dilutions (1/20 and 1/50) were used; for *L. casei* serum dilutions of 1/800, 1/1 330 and 1/2 000 were used, but if normal growth was evident in the 1/800 dilution a control test with a dilution of 1/20 was carried out. 3. FIGlu excretion expressed in micromol/hr.

Case reports

Case 1. A gravida-2 had previously enjoyed fairly good health and had had a normal delivery in 1959. During her second pregnancy she had sought advice for vaginal bleeding in the second month. The uterus increased rapidly in size to the level of the navel, and hysterotomy was performed for a probable hydatid mole.

Histologic examination revealed no signs of malignancy, and the layers of cytotrophoblasts and syntrophoblasts had an ordinary arrangement. Repeated gynaecologic control tests were carried out and histaminase titer determinations were done at 2-week intervals. As the bleeding recommenced 7 weeks after the hysterotomy, curettage was performed.

Histologic examination of the biopsy specimen now revealed chorionic epithelial vegetations composed mainly of cytotrophoblasts with all the signs of proliferative capacity, but there were no morphologic features suggesting choriocarcinoma (Fig. 3). As the plasma histaminase values became progressively higher, and as lesions of the lung parenchyma compatible with tumour metastases were observed, a clinical diagnosis of chorionepithelioma was made and the patient was remitted for treatment.

Case 2. A para-2, aged 25, had previously been healthy and had had two normal deliveries in 1961 and again in 1962, 3 weeks before she fell ill. The last delivery had been normal except

for retention of remnants of membrane. She was admitted following sudden profuse bleeding, and immediate curettage was performed.

Histologic examination indicated a malignant chorionepithelioma of the choriocarcinoma type (Fig. 4) and roentgenography of the lungs revealed widespread bilateral lesions, probably metastases. The patient was transferred for treatment.

Tests

The results of the microbiologic titrations for folic acid inhibitory factors in whole blood and in serum are indicated in the figures by dark squares for inhibition of growth, while the white squares show normal growth of bacteria in corresponding dilutions. The urinary values of FIGlu excretion after a histidine load are expressed in micromol/hr. The mean for healthy adults is 12 micromol/hr.

The findings in Case 1 are given in Fig. 5. Neither in whole blood nor in serum were any growth-inhibiting factors observed at the commencement of treatment. Such factors appeared in the serum immediately after methotrexate therapy had been started and decreased again relatively rapidly when the drug was discontinued. The elimination took place at an increasingly slow rate, however, with increasing number of treatment courses, probably owing to the fact that the organism had become saturated. The inhibitory factors had disappeared from the serum before the peak was reached in the whole blood.

Growth-inhibiting factors were first noted in the whole blood on the eighth day and reached the peak value on the tenth day. Four weeks after treatment, inhibition of growth had been eliminated for *Streptococcus faecalis* but for *Lactobacillus casei* inhibition was still noted in a dilution of 1 in 20. The same phenomenon was noted for the whole blood as for the serum, namely retardation of elimination with increasing number of courses, indicating saturation of the organism after the third course.

The results of the microbiologic determinations in Case 2, which were continued over a period of five months, are shown in Fig. 6. This case is thus a suitable one for a discussion of the effect of the growth-inhibiting factors. As in Case 1, the effect appeared rapidly in the serum, and quickly disappeared before the peak level had been reached in the whole blood.

A growth-inhibiting effect was first noted in the whole blood on the eighth day; it reached the peak level on the tenth day and began to subside after three weeks. When therapy was continued, the inhibitory effect of the blood corpuscles persisted for a longer period but a definite decrease was observed between the third and fourth, and the fourth and fifth periods where the pause in the therapy had lasted for 27 and 35 days, respectively. After the last course of treatment inhibitory factors were completely absent for *S. faecalis* but were still weakly active for *L. casei* in a dilution of 1 in 20.

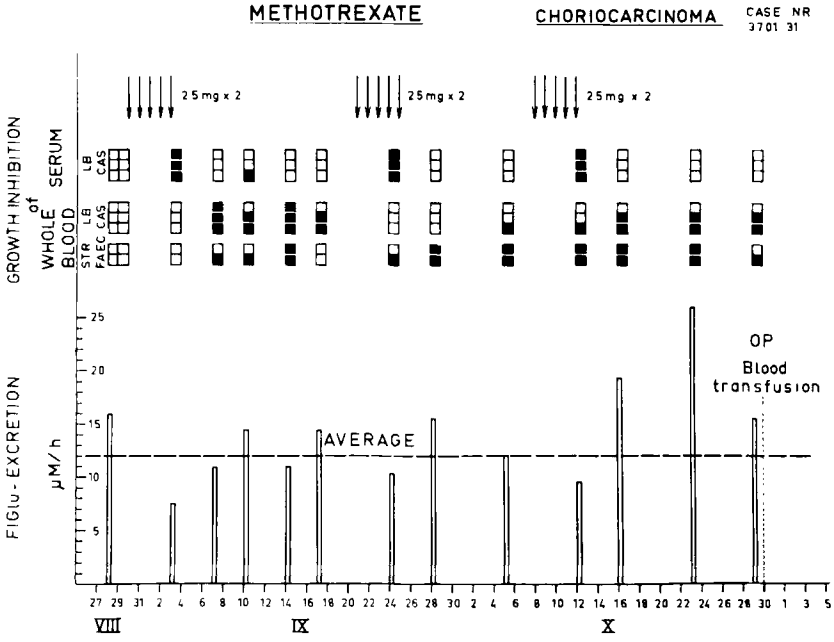


Fig. 6. Case 2. Microbiologic estimations and FIGlu assays. 1. Serum FA. *L. casei* and serum dilutions of 1/20, 1/80 and 1/400 were used. 2. Whole blood FA. *S. faecalis* and *L. casei* were used. For *S. faecalis* two serum dilutions (1/20 and 1/50), and for *L. casei* serum dilutions of 1/800, 1/1 330 and 1/2 000 were employed. 3. FIGlu excretion expressed in micromol/hr.

As in Case 1, no significant rise or fall in the urinary FIGlu values was noted, but a certain degree of undulation could be observed between minimum values in association with high serum folic acid levels and peak values with high whole blood levels.

Abnormally elevated histaminase titers (Fig. 7) were noted at an early stage in Case 1; they fell slightly after hysterotomy but rose again later. They showed a slight relative decrease after the curettage although in absolute figures they were still elevated; they returned to normal with commencement of methotrexate therapy. No pathologically elevated histaminase values were noted in Case 2.

Neither quantitative nor qualitative tests revealed any signs of chorionic gonadotrophin in the urine in Case 1 but elevated titers were still obtained after the fourth course of treatment in Case 2 (Fig. 8). A fifth course was given as the patient still had pulmonary lesions that appeared to be metastases; following this, no HCG was found in the urine, not even in the qualitative tests.

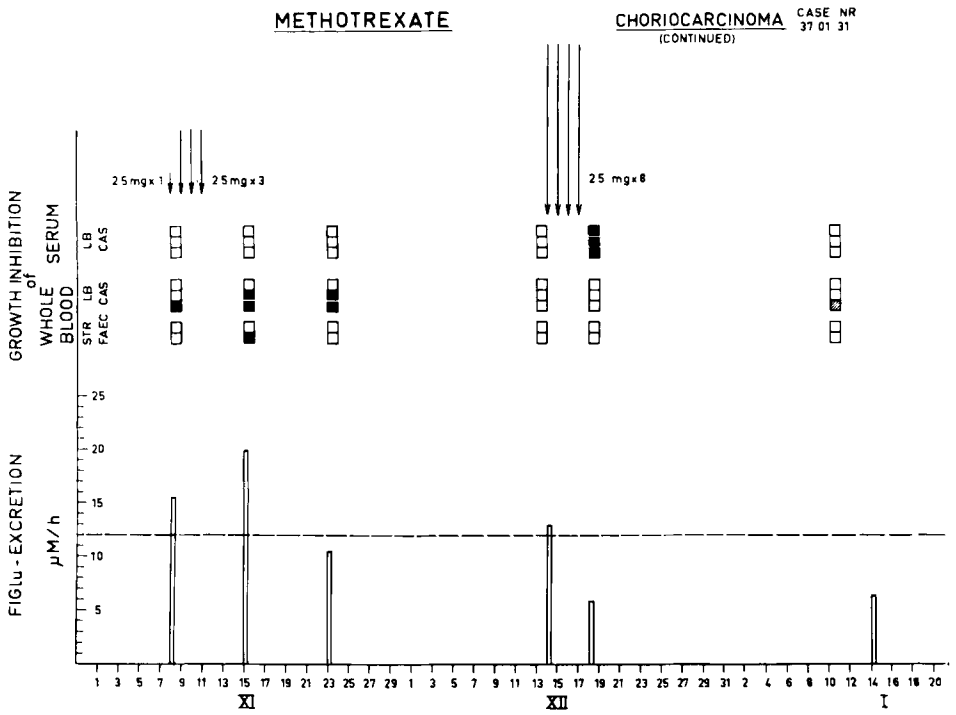


Fig. 6 (Right-hand part).

No significant effects on the haematopoiesis were noted in Case 1 as a result of methotrexate therapy. In Case 2, as may be seen from the curve, inhibition of the white blood cell and thrombocyte regeneration was first noted in connection with the fifth course of treatment, in which 20 mg daily were given.

A few words might be said about the morphologic effects of methotrexate therapy. Several of the members at the Symposium in London in 1962 stated that it was difficult to obtain morphologic evidence of the effect of methotrexate chemotherapy on tumours. Our pathologist (HILD HANSSON) compared in Case 2 the microscopic appearances after the operation with those seen before the commencement of chemotherapy. The following changes were noted after methotrexate treatment. The cytoplasm was disintegrated and the syncytiotrophoblasts disrupted. The chromatin was split up into small grains and the nuclei showed fragmentation. Another investigation on a larger series of cases is being planned to ascertain whether these changes are specific to the chemotherapeutic effect.

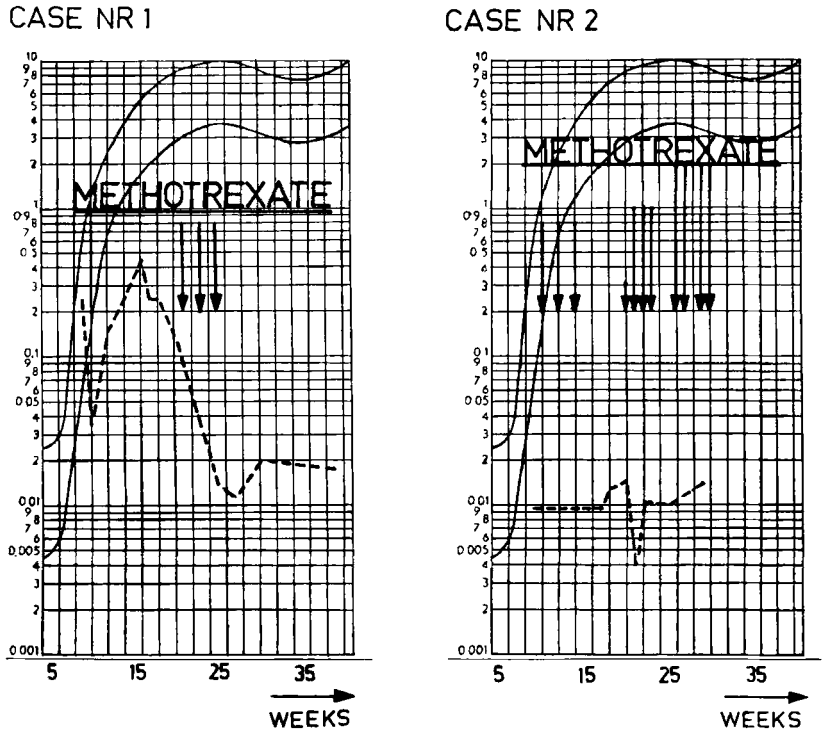


Fig. 7. Histaminase activity in plasma. Time recorded in weeks along the X axis. Concentration expressed in gamma/ml/hr and recorded in log terms along the Y axis. The normal range in pregnancy is indicated.

Roentgenologic appearances

The angiographic appearances in these rare forms of tumour have been described earlier by BORELL, FERNSTRÖM & WESTMAN (1955, 1958) and by BORELL & FERNSTRÖM (1961). The angiographic changes in the few cases reported consisted in hypervascularization of the uterus, especially at the tumour site, irregularly delimited cavities, and the occurrence of arteriovenous fistulas in the tumour. These investigators had not observed changes of this type in any other form of uterine tumour, nor in cases of normal intra-uterine pregnancy. Neither had they observed them in the puerperium, nor after abortion, and in consequence they considered such changes to be typical of this form of tumour.

Pelvic angiography was carried out twice in the two cases now reported at an interval of a month between the two examinations. Satisfactory contrast filling of the pelvic vessels was obtained without compression of the femoral

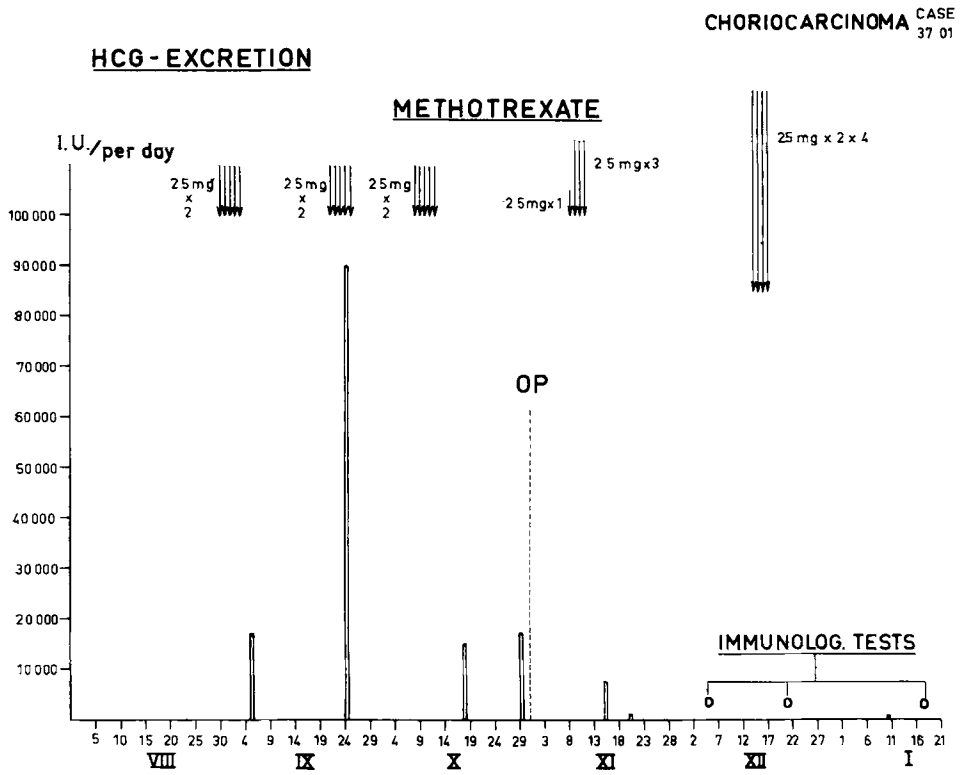


Fig. 8. Case 2. Quantitative and qualitative estimations of human chorionic gonadotrophin in urine. Time recorded along the X axis and excreted amounts of HCG, expressed in I.U./day, along the Y axis.

arteries by using a modification of FERNSTRÖM's (1955) technique with bilateral insertion of catheters. Roentgenographic examination of the lungs was also undertaken repeatedly. The time relationships between roentgen examinations, chemotherapy, and operation, are collected in Fig. 11.

The first angiographic examination in Case 1 (Fig. 12) revealed greatly dilated uterine and ovarian arteries on the right side, with rapid filling of a highly vascularized area in the fundus uteri, very rapid filling of wide veins, suggesting the presence of arteriovenous fistulas, and hypervascularization of the entire uterus. The same changes were seen at the second examination (Fig. 13) except that the vascularized area was now less extensive, the uterine arteries were less dilated and the venous outflow had definitely decreased.

The first lung roentgenogram, made at the patient's district hospital 14 days before her admission to us, showed a metastasis-like change at the base of the

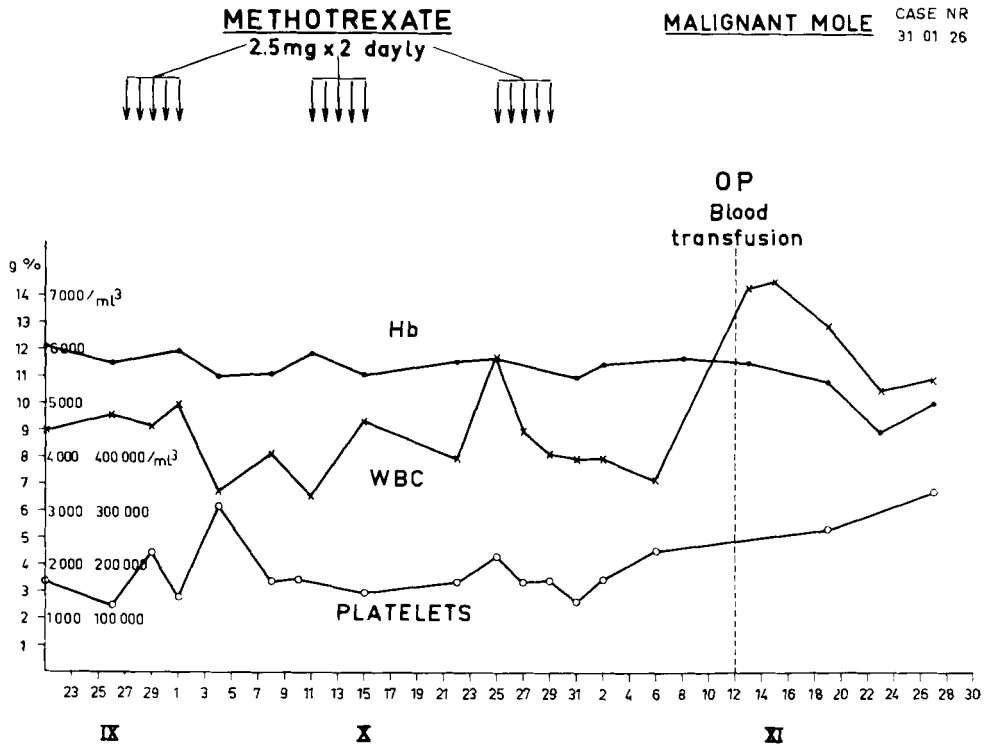


Fig. 9. Blood counts in Case 1. Hemoglobin expressed in g %, WBC in 1 000/ml³, and platelets in 100 000/ml³.

right lung (Fig. 14). This lesion was no longer evident at the next examination, nor were there any pathologic changes in subsequent lung roentgenograms.

Both angiographic examinations in Case 2 disclosed mild hypervascularization of the uterus, with weak contrast-filling in the fundus area, but there were no changes of the type that have been described as characteristic (Fig. 15). Multiple metastases were present in the lungs from the beginning (Fig. 16). Definite regression was noted in a roentgenogram immediately after three periods of chemotherapy (Fig. 17); this became more marked after surgery, and at the end of the methotrexate treatment all signs of metastases had disappeared (Fig. 18).

Comment. The angiographic changes in Case 1 tallied well with those described by BORELL, FERNSTRÖM & WESTMAN (1955, 1958). They were not so marked at the second examination (A 2 in Fig. 11). A regression of this type has not previously been seen in angiograms in this form of tumour. BORELL

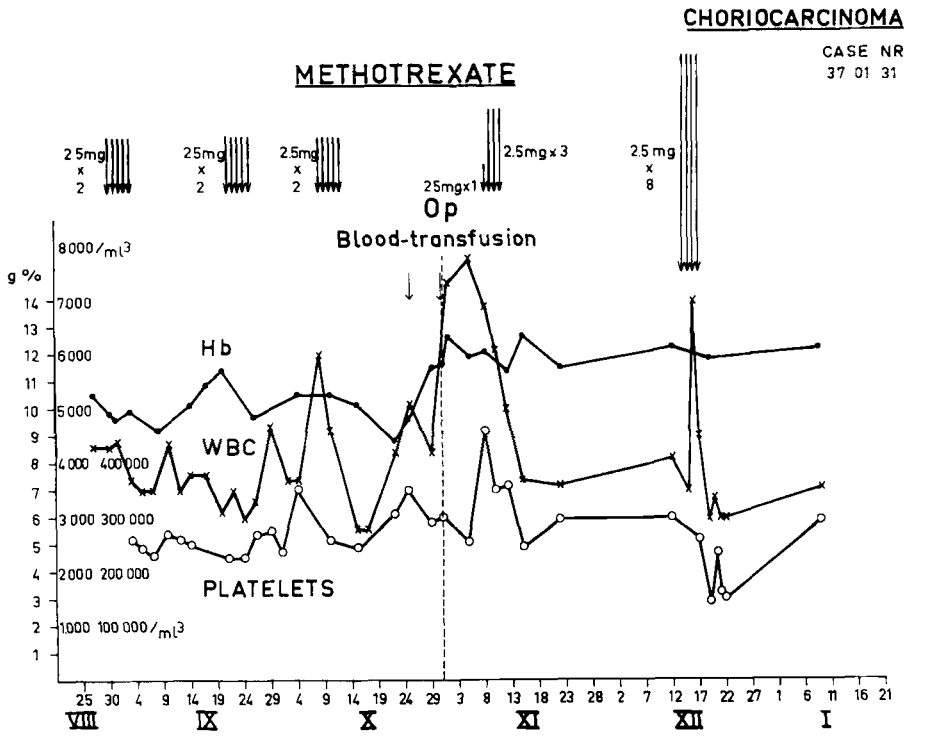


Fig. 10. Blood counts in Case 2. Hemoglobin expressed in g %, WBC in 1 000/ml³, and platelets in 100 000/ml³.

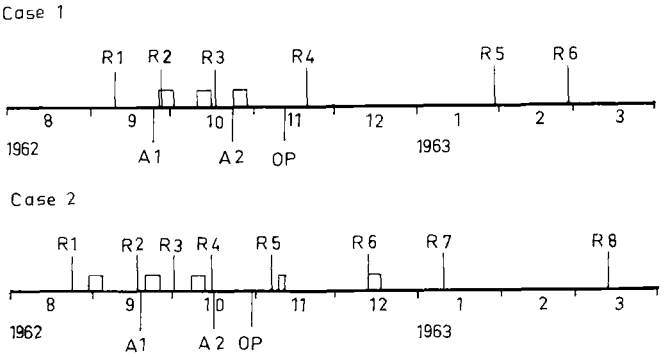
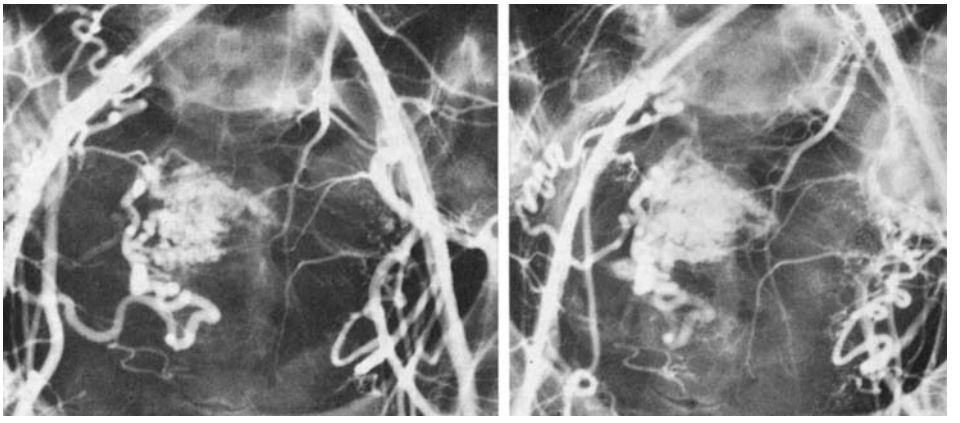


Fig. 11. Time relationship of roentgen examinations to chemotherapy and operation, August 1962 to March 1963. R = lung roentgenography. A = angiography, OP = operation. Rectangles indicate chemotherapy.



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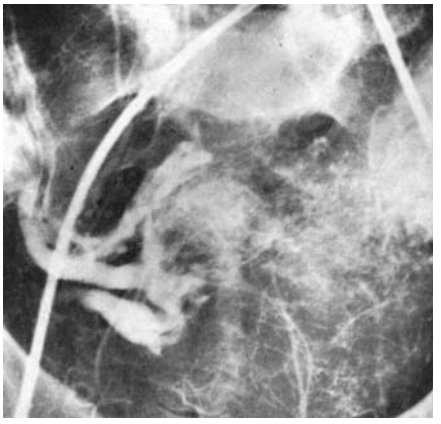

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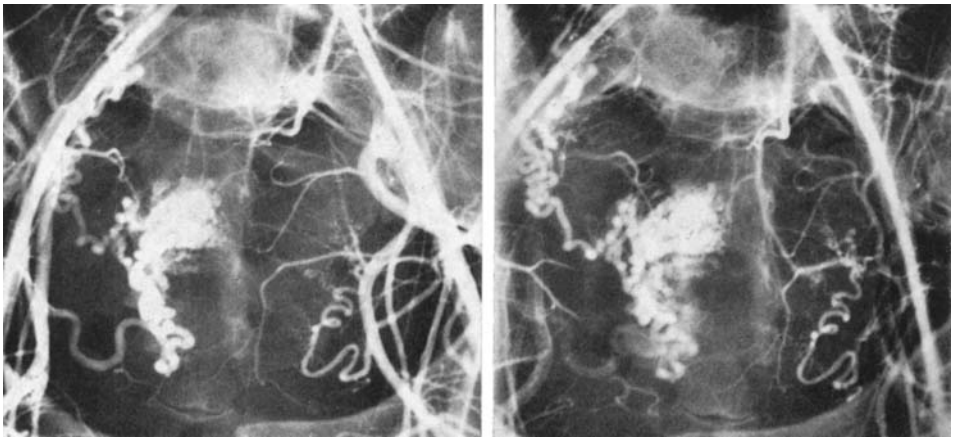
Fig. 12. Case 1. First angiographic examination (A 1 in fig. 11). a) 1 sec after injection of contrast medium. Both uterine arteries and the right ovarian artery clearly visible. Highly vascularized tumour visible in fundus of uterus. b) 0.5 sec later (a and b form a stereopair). The vascularized tumour now well filled. c) 2 sec later. Most of the contrast medium has now passed into widely dilated veins.

et coll. (1955), who carried out two angiographic examinations separated by 9 days in a case of destructive mole, considered that an increase in the vascular changes had taken place during that short period. In view of the great variation in the macroscopic, and above all in the microscopic, appearances of placental tumours it is not surprising that no typical vascular changes were seen in Case 2. As BORELL et coll. (1955) have also pointed out, many cases will probably not be diagnosable with pelvic angiography. It should also be borne in mind that, as the first angiography in Case 2 (A 1 in Fig. 11) was performed two weeks after the first course of chemotherapy, earlier, small, but characteristic changes may conceivably have disappeared.

The pulmonary lesion in Case 1 disappeared before any treatment had been



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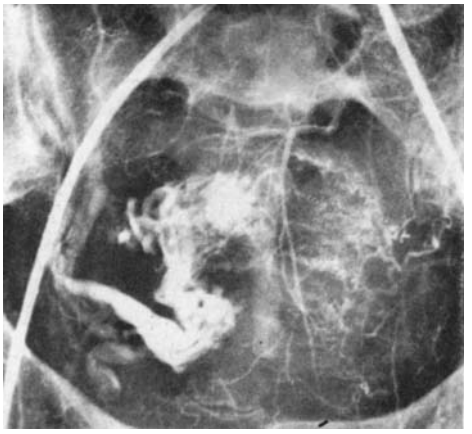

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Fig. 13. Case 1. Second angiographic examination (A 2 in fig. 11). Same angiographic phases as in fig. 12.

applied. While there may, of course, have been some other explanation for the lesion than metastasis, it is nevertheless known that metastases do sometimes disappear spontaneously in this form of tumour. The pulmonary metastases in Case 2 regressed steadily during chemotherapy prior to the operation. They disappeared completely after a final course of chemotherapy given 1 1/2 months after surgery.

Discussion

One of these cases was a malignant destructive mole and the other a choriocarcinoma. An increasing plasma histaminase concentration was noted in the

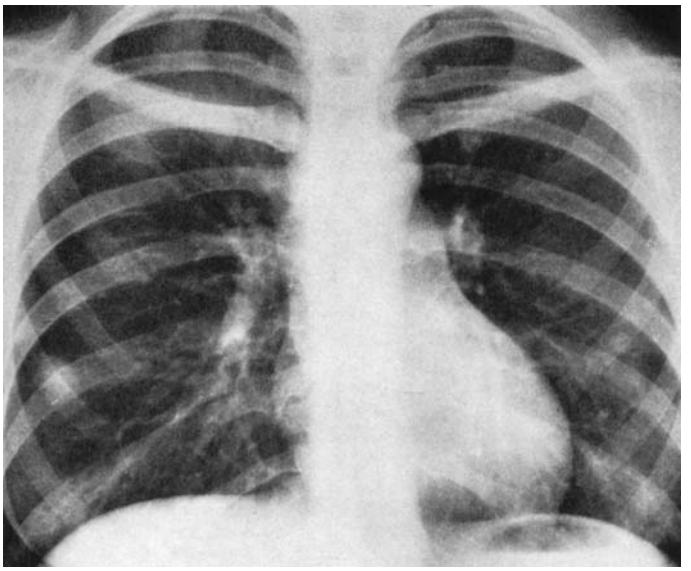

Fig. 14. Case 1. Lung roentgenogram (R 1 in fig. 11). A lesion resembling a metastasis is visible in the right lung.

former case but on the other neither quantitative nor qualitative immunobiologic assays yielded any signs of chorionic gonadotrophin in the urine. Lung roentgenograms showed changes pointing to metastases, and numerous arteriovenous sinuses were noted at pelvic arteriography. In the choriocarcinoma case the plasma histaminase level was normal but an increasing concentration of HCG was found in the urine. Progressive metastatic lesions were observed in the lungs, but there were no signs of arteriovenous sinuses at pelvic arteriography.

According to the evidence from the microbiologic titrations during methotrexate therapy, growth-inhibiting factors appeared rapidly in the serum in both cases and were then rapidly eliminated. The maximum level for growth inhibition in the whole blood fraction, on the other hand, was first noted on the eighth to tenth day; the incorporation of the folic acid antimetabolite thus showed the same pattern of behaviour as other substances (Fe for instance) that are incorporated at the blast stage and run parallel with crythrocyte maturation. Case 2 is an especially good illustration of how the uptake of the growth-inhibiting factor had already begun to diminish before the next course of treatment was started. There is thus a 'messenger principle' which during these intervals eliminates the antimetabolite from the reproduction seat in the bone

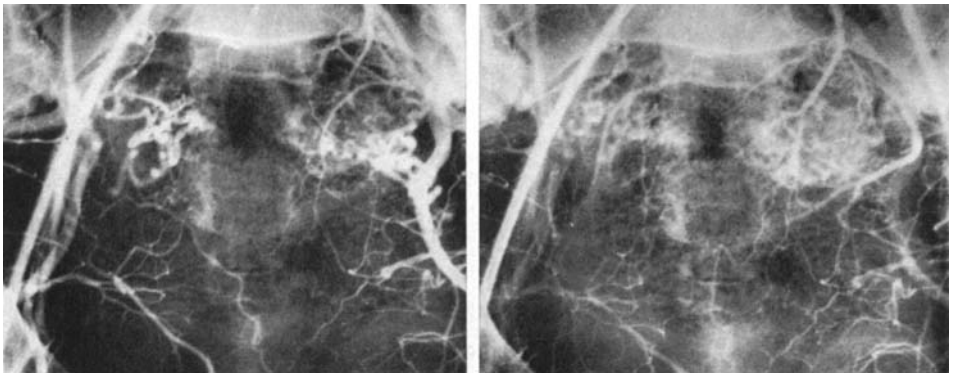

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Fig. 15. Case 2. Angiographic examination (A 1 in fig. 11). a) 2 sec after injection of contrast medium. b) 1 sec later.

marrow before the next therapeutic course is begun. No such behaviour can conceivably take place within the tumour cell, where the antimetabolite probably accumulates instead. There is reason to believe that it is this situation that produces the irreversible antineoplastic effect and, with suitably chosen doses and treatment intervals, the reversible marrow effect. Signs of generalized saturation of the organism, both intracellular and extracellular, were however observed after the third course; this suggests that caution is necessary and that a slightly longer interval should be chosen if therapy needs to be continued.

The urinary FIGlu titers during methotrexate therapy showed, it is true, no significant changes, but they did reveal a definitely undulating tendency, with minimum values in association with high serum folic acid concentrations, and with maximum values when the L. casei inhibition in whole blood was high. Thus in connection with the intracellular incorporation of the antimetabolite with THFA blocking there was an increased excretion of formiminoglutamic acid after a histidine load. Another remarkable feature is that these tumours appear to be associated with low absolute figures for FIGlu excretion.

The serum vitamin B_{12} values lay within the normal range, and there were no signs of toxicity in the sternal marrow.

The plasma histaminase titer became normal during methotrexate therapy in the patient with an invasive mole. As GREENSTEIN (1954) has already pointed out, it is always necessary in enzymologic studies to distinguish between enzymatic changes arising because of the progression of the growth and those that may be a result of the response of the host organ to the tumour

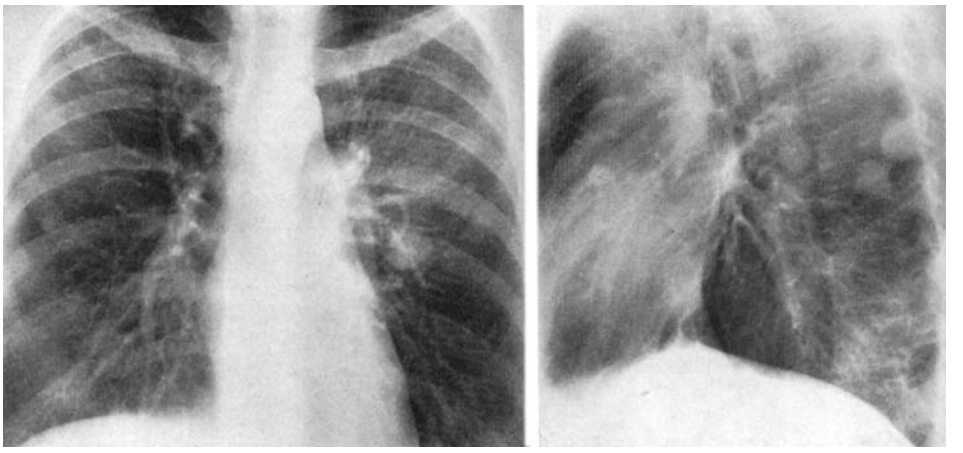

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Fig. 16. Case 2. Lung roentgenogram (R 1 in fig. 11). Frontal and lateral projections. Multiple metastatic lesions.

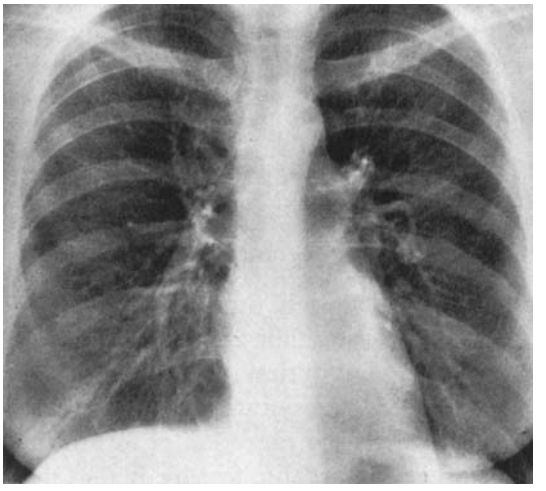
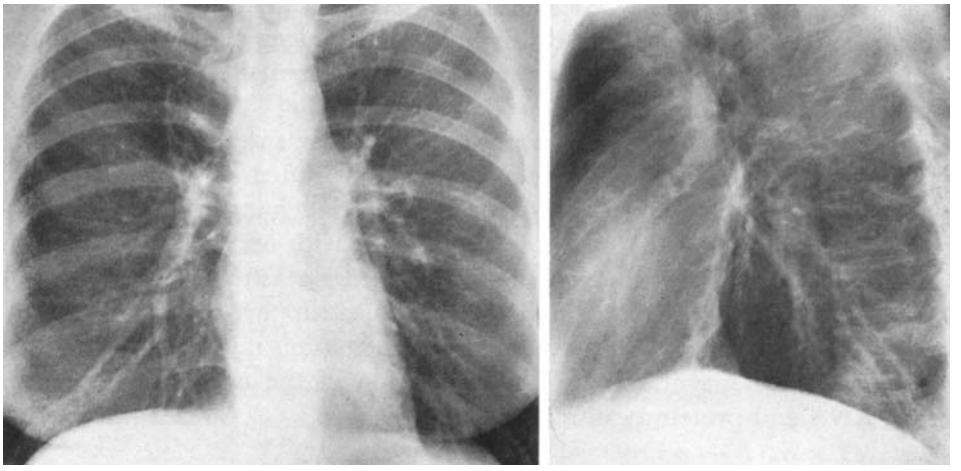


Fig. 17. Case 2. Lung roentgenogram (R 4 in fig. 11). The metastatic lesions have regressed.

infiltration. Just as the histaminase reaction, which is provoked by the maternal decidua, is to be regarded as a defence against the enormous production of histaminase by the foetus (SWANBERG 1950), so the heightened histaminase reaction, occurring in association with the development of an infiltrating and destructive mole, should probably be interpreted as a defence system. This would also explain why this exophytically growing choriocarcinoma, which



a b

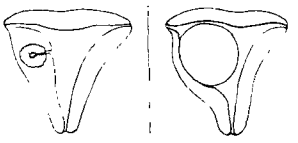
Fig. 18. Case 2. Lung roentgenogram (R 7 in fig. 11). Frontal and lateral projections. The lesions are no longer visible.

develops from other tissue elements, does not produce this reaction but instead causes a sharp increase in the hormone-producing elements, with increased excretion of HCG in the urine as a result. Intermediate variations of every conceivable type may of course be represented between these two 'pure' extremes. In view of the dual origin of the trophoblastic tumours, the investigation must however always include a study of both these characteristics; such a study should also be continued when the disease is being followed during and after methotrexate therapy, and for up to one year after the treatment. Discrepancies in the opinions concerning the treatment and prognosis in these tumours (HERTIG & SHELDON 1947, NOVAK 1947, KOTTMEIER 1943) could undoubtedly be avoided if more complete investigations were made.

The total dose of methotrexate was 75 mg in the case of malignant mole and, in response to this, all signs of the growth disappeared. No irreversible damage to the bone marrow or the haematopoiesis could be observed in connection with the treatment. In the choriocarcinoma case the total dose amounted to 180 mg; depression of the haematopoiesis was observed in this case in connection with the final course of treatment involving 4 daily doses of 20 mg. This observation suggests that with this dose the danger zone is being approached, a fact which may explain the irreversible marrow damage that has been observed earlier in connection with courses of 100 mg. It would appear to the authors that courses exceeding 80 mg should be avoided; it would seem

better to give another course after a further 2 weeks if signs of tumour are still present. The courses should be continued until all signs of the growth have disappeared, and control examinations should be carried out for at least a year after the last treatment.

The comparative morphologic study of the biopsy specimen taken before methotrexate treatment and of the operation specimen obtained after the treatment revealed "marked, apparently regressive changes in the syncytiotrophoblastic layer in a few places in the tumour with nuclear fragmentation and here and there signs of cytoplasmic disintegration as well". This observation is interesting inasmuch as it would appear to support the theory underlying methotrexate therapy; the nuclear fragmentation might be interpreted as a disturbed DNA synthesis and the destruction of the cytoplasm as a disturbed RNA and protein synthesis.



	Malignant mole	Choriocarcinoma
Histaminase production	High	None
Chorion gonadotrophin production	None	High
Arteriovenous sinuses	Well developed	Undeveloped
Pulmonary metastases	Dependent	Independent
FA-dependency	High	High

SUMMARY

Two cases of trophoblastic tumour involving the lungs have been primarily treated with methotrexate. The results were assessed by microbiologic assays, estimations of enzyme levels, hormone titer determinations, roentgen examinations of the lungs, and pelvic angiography, the studies being carried out before, during and after the treatment.

ZUSAMMENFASSUNG

Zwei Fälle von trophoblastischem Tumor der Lungen wurden in erster Hinsicht mit Methotrexat behandelt. Die Resultate wurden mittels mikrobiologischen Methoden abgeschätzt, wie z. B. Enzymmengen, Hormonkonzentrationen, Röntgenuntersuchungen der Lungen, Angiographie des Beckens. Solche Untersuchungen fanden vor und nach Behandlung statt.

RÉSUMÉ

Deux cas de chorio-épithéliome avec métastases pulmonaires ont été traités d'embleé par le méthotrexate. Les résultats ont été jugés par des tests microbiologiques, des estimations des taux d'enzymes, des déterminations de titres hormonaux, des radiographies pulmonaires et des angiographies pelviennes, pratiqués avant, pendant et après le traitement.

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