

child, and of the rest all except two gave their reasons for not wanting another as age or size of family, so that in only two cases did the experience of labour make the patient "not very keen to have another."

This shows a very different picture from that given by the 70 patients with no relaxation training, where four (6%) felt no pain or only slight pain in labour; 33% described labour as a pleasant sensation, and 24% found labour unpleasant, and 26% of those not wanting another child gave the labour as their reason.

In the physiotherapy group trained by Read's method the subjective impressions of the patients in the first stage of labour lie between the autohypnosis group and the controls, but in the second stage physiotherapy

TABLE VII

Questionary*	Hypnosis Group		Physiotherapy Group		Control Group	
	No.	%	No.	%	No.	%
1. Memory of (a) The whole of labour ..	33	47	58	83	66	94
(b) Part of labour ..	27	39	10	14	4	6
(c) None ,, ,,	10	14	2	3	0	0
2. Pain felt in first stage:						
(a) None ..	32	46	6	8	3	4
(b) Slight ..	22	31	25	36	16	23
(c) Moderate ..	12	17	32	46	33	47
(d) Severe ..	4	6	7	10	18	26
3. Pain felt in second stage:						
(a) None ..	17	24	0	0	2	3
(b) Slight ..	20	29	2	3	2	3
(c) Moderate ..	19	27	19	27	20	29
(d) Severe ..	14	20	49	70	46	65
4. Was labour (a) Pleasant ..	49	70	16	23	23	33
(b) Unpleasant ..	7	10	24	34	17	24
(c) Not sure ..	14	20	30	43	30	43
5. What about having more children?						
Are you (a) Keen ..	59	84	31	44	35	50
(b) Not keen ..	9	13	36	52	22	31
(c) Definitely against ..	2	3	3	4	13	19
Reasons for 5b or c:						
Labour was too unpleasant ..	2	3	14	20	9	13
Family large enough ..	4	6	22	31	23	33
Age (over 40) ..	7	10	3	4	3	4

\* Similar to the questionnaire used at the Mile End Hospital, London.

training did not appear to alleviate pain or make the labour seem more pleasant to the patient.

Perhaps the greatest subjective gain was that in the autohypnosis group: 70% described the labour as pleasant, whereas only 23% of the physiotherapy patients and 33% of the controls looked back on labour as pleasant.

Summary

The labours of 70 patients trained in autohypnosis are compared with 70 patients given physiotherapy training for labour and 70 control patients.

A statistically significant reduction in the duration of the first stage of labour occurred in the autohypnosis-trained group as compared with the other two groups (P<0.001).

Autohypnosis was found to be an effective analgesic in labour: 59% of this group of patients required no chemical analgesia in any stage of labour, whereas in the control group only 1.4% required no analgesic drug, and in the physiotherapy group all patients required some chemical analgesia. Statistically this difference was very significant (P<0.001).

No significant difference in the third-stage blood loss was found in the three groups.

The episiotomy or tear rate was less in the hypnotically relaxed patients—51% as compared with 73% in the physiotherapy group and 64% in the control group—but this difference is not statistically significant (P=0.10-0.20).

The subjective impression of labour was much more pleasant in the autohypnosis group.

The time spent antenatally (1½ hours for six patients) and the personal attention involved are well worth while to produce such objective and subjective benefits to the pregnant woman, and hypnosis should be used in obstetrics more widely than it is at present.

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CHORIONEPITHELIOMA

A STUDY OF 41 CASES

BY

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A chorionepithelioma is a neoplasm consisting of both syncytial and Langhans trophoblasts in varying proportions. Microscopically, columns and sheets of trophoblasts are seen penetrating the muscle and blood-vessels in a lawless manner interspersed with areas of clotted blood. The most important diagnostic sign of chorionepithelioma is complete absence of a villous pattern. Although Acosta-Sison (1949) saw no fewer than 142 cases of chorionepithelioma during 10 years at Manila, Hall (1950) saw only two in 20 years, Hunter and Dockerty (1955) reported 12 cases in 17 years, and Jones (1954) estimated the incidence as 1 in 70,000 deliveries.

From July, 1953, to December, 1961, a period of eight and a half years, 54,555 deliveries were undertaken by the Department of Obstetrics and Gynaecology, Hong Kong University. In the same period 41 cases of chorionepithelioma were encountered, thus giving an incidence of 1 in 1,331. This relatively high number is misleading and can be explained by the fact that the patients suffering from chorionepithelioma and referred

to the University Unit for treatment were selected from a larger area than that from which the obstetric cases originated. There were altogether 110,409 deliveries in the Colony in 1961, and if abortions and ectopic pregnancies are included the total number of pregnancies was 116,054. In the same year there were 19 cases of chorionepithelioma, thus giving an incidence of 1 in 5,882 deliveries and of 1 in 6,250 pregnancies, still a much higher incidence than most of those reported elsewhere.

### Clinical Features

The average age found by most authors was 30 to 33 years (Teacher, 1903; Chevalier, 1954; Hunter and Dockerty, 1955; Smalbraak, 1957). It is 32.1 years in this series, the youngest patient being 22 and the oldest 48, with 16, 19, and 6 cases in the third, fourth, and fifth decades respectively.

As the 41 women had had altogether 155 deliveries, 20 abortions, 23 moles, and one ectopic pregnancy (a total of 199 previous pregnancies), the average number of previous pregnancies was 4.85.

Kinnunen (1952) found that in his series of 12 cases of chorionepithelioma five followed a mole, four a delivery, and three an abortion. According to Hertig (1950), 50% of cases of chorionepithelioma were preceded by a mole, 25% by an abortion, 22.5% by a delivery, and 2.5% by an ectopic pregnancy. In the present series, 18 (43.9%) were preceded by a mole, 12 (29.3%) by an abortion, 10 (24.4%) by a delivery, and one (2.4%) by an ectopic pregnancy.

The time interval between the last pregnancy and the diagnosis of chorionepithelioma varied between two weeks and four years. It was six months or less in 14 (77.7%) of the 18 cases which followed a mole, but in only eight (36.3%) of the 22 cases which followed an abortion or a delivery.

Vaginal bleeding, continuous or irregular, and lasting for periods varying from two days to one year, occurred in 36 (87.8%) cases, respiratory symptoms (cough, haemoptysis, and chest pain) in 19 (46.3%), abdominal pain in seven (17.1%), and cerebral symptoms in six (14.6%). Rarer symptoms included anorexia, anaemia, dysuria, mass protruding from vagina, and abdominal distension.

The uterus had already been removed in four cases. It was found to be normal in size in nine (21.9%) cases, and enlarged to the size of eight to 24 weeks' pregnancy in 28 (68.3%) cases. Though unilateral or bilateral luteal cysts of the ovaries were present in 15 (36.6%) cases, only four were palpable on vaginal examination. Metastases were found on inspection at one time or another in the vagina in seven cases, in the vulva in five, in the cervix in three, and in the skin in three.

Though a positive hormonal reaction indicates the presence of viable chorionic tissue, one cannot be certain whether the latter is benign or malignant. On the other hand, a negative hormonal reaction is not definitive proof of the absence of a chorionepithelioma. In this series the male frog test was found to be persistently negative in three (7.3%) cases. This had been attributed by Meyer (1931) to the presence of a thick fibrinoid layer preventing the hormones produced from entering the blood-stream, and to a very low hormone production by other investigators. An increased production of chorionic hormone, as evidenced by a positive male frog test, was found in 37 (90.2%) cases, but the amounts as

shown by the highest titre obtainable were, on an average, smaller than those found in molar pregnancies.

Pulmonary secondaries, as revealed by radiological examination of the chest, were found at one time or another in 29 (70.7%) cases.

As to the use of curettage as a method for arriving at a diagnosis of chorionepithelioma opinions diverge considerably. The absence of chorionic tissues in the curettings may be misleading, as the malignant growth may be located deeply in the uterine wall beyond the reach of the curette. Curettage may, however, reveal the presence of chorionic tissue, thus giving the first clue to the diagnosis even at a time when hormone assays are still indeterminate. Some authors (Hitschmann, 1928; Mathieu, 1939; van Bouwtdijk Bastiaanse, 1938, 1956) have warned against the use of the curette in cases of possible chorionepithelioma for fear of promoting haematogenous dissemination and thus giving rise to the development of widespread metastases. It may also result in intractable bleeding, perforation of the uterus, local infection, and general sepsis. These dangers may well have been exaggerated, as dilatation and curettage were performed on one or more occasions in 11 cases in this series without any apparent mishaps. Chorionepitheliomatous tissues were obtained in six, normal endometrium in four, and nothing whatsoever in one. No primary growth was found in the uterus in two cases where normal endometrium was obtained. One or multiple lesions were found in the other nine cases, and were therefore missed by the curette in three.

Of the 40 cases of chorionepithelioma, excluding the case of tubal chorionepithelioma, four had the uterus removed before the development of chorionepithelioma, one patient refused operation and was lost trace of, and a primary uterine lesion was present in 31 and absent in four.

Of the 19 deaths, post-mortem examination was done in 17. Metastases were found in the lungs in all the 17 cases: in the brain in 13, in the gastro-intestinal tract in 11, in the kidneys in seven, in the pelvic structures (uterus, vagina, pouch of Douglas, parametrium) in seven, in the spleen in five, in the mesenteric or mediastinal lymph nodes in three, on the skin in three, and in the thyroid in one. The cause of death was marked cachexia in nine, cerebral haemorrhage in six, haemoperitoneum (due to rupture of liver metastases) in one, and generalized peritonitis in one.

### Treatment

No treatment whatsoever was given to seven of the patients in this series: one refused operation and was discharged against medical advice, five were too ill to receive any form of treatment and died within a short time after admission, and one, who was seen in 1958 and had had her uterus removed previously for a molar pregnancy, lived for five months after the diagnosis of chorionepithelioma had been made, and would have been given courses of methotrexate but for the fact that we did not start to use methotrexate until January, 1960. The one who refused operation was lost trace of and the other six died.

Hysterectomy with or without removal of the appendages was performed in 29 cases. It was the sole form of treatment in 13, combined with radiotherapy (deep x-ray therapy in four, deep x-ray therapy and local application of radium in one, and radium alone in

one) in six cases, and used in association with methotrexate in 10. Ten are dead, seven cannot be traced, and 10 (29.3% of the whole series or 41.4% of the group treated with hysterectomy) are at the time of writing apparently well with no evidence of active disease.

Radium application alone was given to a patient who had a secondary lesion in the vagina one month after a hysterectomy for a molar pregnancy. She could not be traced after having returned for follow-up for eight months.

Testosterone was given to one patient who had cerebral and respiratory symptoms. There was no response and she died within a month.

Methotrexate alone was given to two patients who were admitted in the terminal stage with cerebral symptoms. Both died within two weeks—one after a course of methotrexate and the other after six doses.

The case of tubal chorionepithelioma was treated by salpingectomy. The patient returned for follow-up for five months and since then could not be traced.

Of the 41 patients with chorionepithelioma in this series, 19 (46.3%) have died, 10 (24.4%) cannot be traced, and 12 (29.3%) are apparently well with no sign of disease. Even though the number is small, it is obvious that radiotherapy does not improve the results. Indeed, it has been very disappointing in our experience. Of the 19 cases treated by hysterectomy with or without radiotherapy, seven were well, giving a percentage "survival" of 36.8% (for periods varying from two to seven years). Of the 10 cases treated by hysterectomy and methotrexate, five were well for periods varying from 10 months to four years, giving a percentage "survival" of 50%. It therefore seems that methotrexate does not significantly improve the results. But unknowingly, and at times purposely, methotrexate was given to a group which was relatively less favourable.

It is shown in Table I that while two-thirds of those with no radiological evidence of pulmonary metastases remained well, only one-seventh of those with positive findings were so, and that, on the whole, the older the patient the worse the prognosis. It can be seen from Table II that the group treated with hysterectomy and methotrexate consisted of a relatively larger proportion of patients who had positive radiological findings in the chest and who were slightly more advanced in age. The results, however, were none the worse in this less

TABLE I.—Relationship Between Prognosis and Pulmonary Secondaries and Age

		Dead	Lost	Well
X-ray chest:				
Pulmonary secondaries absent ..			4	8 (66.6%)
" present ..		19	6	4 (13.8%)
Age	{ 20-29 .. .. .	5	4	7 (43.8%)
	{ 30-39 .. .. .	11	4	4 (21.1%)
	{ 40-49 .. .. .	3	2	1 (16.6%)

TABLE II.—Comparison of Incidence of Pulmonary Secondaries and Age Distribution in the Two Groups of Patients Treated by Hysterectomy with and without Methotrexate

	Hysterectomy with or without Irradiation		Hysterectomy and Methotrexate		
	No.	%	No.	%	
X-ray chest:					
Pulmonary secondaries absent ..					
" present ..					
Age	{ 20-29 .. .. .	9	47.4	1	10
	{ 30-39 .. .. .	10	52.6	9	90
	{ 40-49 .. .. .	9	47.4	4	40
	{ .. .. .	9	47.4	4	40
{ .. .. .	1	5.2	2	20	

favourable group, hence confirming the impression that we have found in methotrexate a useful drug in the treatment of chorionepithelioma.

Altogether 12 cases were treated with methotrexate, 10 in combination with hysterectomy. The details are listed in Table III. A description of the scheme of treatment used and summaries of the first seven cases treated—namely, Nos. 2, 3, 4, 6, 7, 11, and 12—are given in the following paper (Chan, 1962). One course or less had been given to three terminal cases; the patients who died before any more could be given.

TABLE III.—Summaries of 12 Cases Treated with Methotrexate

Case No.	No. of Courses	Total Dosage (mg.)	Interval (wk.)	Male Frog Test		X-ray Chest		Results
				Highest Titre Before Treatment	After Treatment	Before Treatment	After Treatment	
1	3	280	2	+	-	-	-	Well 48 months
2	5	340	2	+	-	+	-	Well 28 months
3	5	495	2	+	-	+	-	Well 23 months
4	7	700	2	1:400	-	+	-	Well 12 months
5	9	725	3	+	-	+	-	Well 10 months
6	2	200	2	+	-	+	+	Lost 2 months
7	6	550	2	+	-	+	-	Lost 4 months
8	6 doses	30	-	+	+	+	+	Dead 2 weeks
9	1	70	-	+	+	+	+	Dead 29 months
10	1	120	-	+	+	+	+	Dead 12 days
11	7	665	2	+	+	+	+	Dead 6 months
12	10	1,105	2	+	+	+	+	Dead 10 months

Two courses were given to one, three to one, six to one, nine to one, and 10 to one. Two cases were given five courses and another two had seven. While stomatitis is the commonest toxic manifestation of any significance, diarrhoea, generalized skin rash, alopecia, malaise, and nausea are also encountered.

The general condition of the patients who responded greatly improved. Though appetite was invariably lost during treatment, it was soon restored after the completion of each course. Every one of the first seven cases put on weight. The male frog test, which was positive in every case, became and remained negative in all the first seven cases. It remained positive, however, in all the five fatal cases: three of them were admitted in their terminal stage and two, after some initial improvement, failed to show any further response and proceeded rapidly to death. Pulmonary metastases, as shown by serial x-rays, underwent marked regression in all the first seven cases. In the last two cases (Cases 11 and 12), the initial favourable response was followed by an increase in number and size of pulmonary secondaries.

Discussion

Opinions on treatment are as varying as they are in regard to other aspects of this subject of chorionepithelioma. While some authors (Hitschmann, 1901; Schmauch, 1907; Gans, 1954), believing that any form of treatment did more harm than good and that spontaneous regression in chorionic tumours was not infrequently encountered (more so than in malignant tumours of any other origin), advocated a conservative attitude; others (Frankl, 1937; van Bouwduijk Bastiaanse, 1938; Richter, 1939) advised the administration of blood

transfusion, using especially blood of pregnant women. The use of hormones in the form of oestrogens (Kullander, 1948; Wirtz, 1951; Barnes, 1954), testosterone (Flynn, 1952), and thyroxine (Perrault *et al.*, 1951), of a pituitary-inhibiting drug, parahydroxy-propiofenone (Perrault *et al.*, 1949; Lepage *et al.*, 1953), of placental extracts as a form of active immunization (Schuster, 1952), of nitrogen mustard (Beecham *et al.*, 1955; Barnes, 1955), or of radioactive phosphorus (Hunter and Dockerty, 1955) had been advocated either in order to strengthen the defensive forces or to exert a destructive influence upon the malignant chorionic elements. None of the above has been convincingly proved to be of any definite value.

Hysterectomy has now become the treatment of choice in cases of uterine chorionepithelioma. It should be done in order (1) to prevent further metastases, (2) to prevent haemorrhage from the uterine lesion which could be continuous and profuse, and (3) to afford confirmation of the diagnosis. Even though some still consider the preservation of the ovaries an inexcusable exposure of the patient to danger, as the ovaries may harbour minor disseminations which may still be grossly unrecognizable but may prove fatal later on, the majority believe removal of the appendages to be unnecessary as chorionepithelioma metastasizes by the blood-stream. The ovary was the site of secondary metastases in only two cases in this series, and in both of them the involvement was grossly obvious at operation. Some even go so far as to regard the castration of a woman as unjustifiable and a serious mistake, for they believe that a woman with well-functioning ovaries possesses in these organs one of the most important protecting sources against a possible pathological increase of vitality and a possible heightening of malignancy of chorionic cells disseminated in the body and present in a state of latency. Unless the ovaries are distinctly affected they should therefore be spared. Luteal cysts should also be left alone.

Radiotherapy had been repeatedly recommended by some authors (Peightal, 1934; Davis and Brunshwig, 1936; Levi and Haig, 1951), but it was more often considered to be of no value by others. There are numerous publications reporting the disappointing result with x rays (Wilson, 1939; Smiley and Clements, 1940; Smith and Werthessen, 1941; de Alvarez, 1942; Kullander, 1948; Dilworth *et al.*, 1950; Mohler and McConnell, 1952; Peel *et al.*, 1955; Beecham *et al.*, 1955).

Surgical technique at present has made it possible to remove metastatic lesions formerly considered inaccessible. Lobectomy (Maier and Taylor, 1947), craniotomy (Dockerty and Craig, 1942; Hunter and Dockerty, 1955), and nephrectomy (Peightal, 1934) were performed with success in cases where there was a solitary metastatic lesion in the lung, brain, or kidney.

In recent years hypophysectomy (Luft *et al.*, 1956) and pituitary ablation with yttrium-90 (Evans *et al.*, 1959; Chambers, 1961) have been advocated for cases of disseminated chorionepithelioma.

Treatment of chorionepithelioma and related trophoblastic tumours with methotrexate with gratifying results in most instances has been reported in recent years (Li *et al.*, 1956, 1957, 1958; Holland, 1958; Hertz *et al.*, 1958; Bagshawe and Brooks, 1959; Buckle, 1959, 1961; Perlson and Whitsitt, 1960; Bagshawe and McDonald, 1960; Manly, 1961; Hreshchysyn *et al.*,

1961; Hamilton, 1962). Methotrexate should be given to every case of chorionepithelioma where there are secondaries in the lungs, brain, vagina, or elsewhere in the body or where the male frog test remains positive after hysterectomy.

### Summary

Forty-one cases of chorionepithelioma were encountered during a period of eight and a half years, from July, 1953, to December, 1961, at the Department of Obstetrics and Gynaecology, Hong Kong University. In the same period 54,555 deliveries were undertaken by the same unit. The incidence of chorionepithelioma was thus one in 1,331 deliveries.

The average age of the patients is 32.1 years and the average number of previous pregnancies 4.85. The majority (43.9%) were preceded by a mole, 29.3% by an abortion, 24.4% by a delivery, and 2.4% by an ectopic pregnancy. The time interval between the last pregnancy and the diagnosis of chorionepithelioma varied between two weeks and four years. Vaginal bleeding, continuous or irregular, was the commonest symptom, and the uterus was enlarged in more than two-thirds of the cases. The male frog test was positive in 37 cases and pulmonary secondaries, as revealed by radiological examination of the chest, were found in 29 cases. The usefulness and danger of curettage are briefly discussed, and common post-mortem findings are given.

No treatment was given in seven cases, radium application alone to one case, testosterone alone to another, and methotrexate alone to two. The case of tubal chorionepithelioma was treated by salpingectomy. Hysterectomy with or without removal of the appendages, which was performed in 29 cases, was the commonest form of therapy. It was the sole form of treatment in 13, was combined with radiotherapy in six, and was used in association with methotrexate in 10. From an analysis of the results methotrexate appears to be a useful adjunct in the treatment of chorionepithelioma.

A review of the literature in regard to the various forms of treatment of chorionepithelioma is included.

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## TREATMENT OF CHORIONEPITHELIOMA WITH METHOTREXATE

BY

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Methotrexate (4-amino-N-10-methylpteroylglutamic acid) is an antimetabolite which interferes with the participation of folic acid (the active principle of folic acid) in nucleic acid synthesis. As the conversion of folic acid to folinic acid is an essential step in the synthesis of nucleic acid, methotrexate, which is an antagonist to folic acid, disrupts the mitotic process. Since malignant cells proliferate rapidly and constantly, thus requiring exceptionally high nucleic acid synthesis and turnover rates, the therapeutic possibilities of artificially induced folic-acid deficiency in malignant processes become apparent. Moreover, it has been shown experimentally in the rat that the tissues of the female genital tract and the foetus have a high requirement for folic acid (Hertz and Tullner, 1949; Nelson and Evans, 1949). The clinical phenomenon of macrocytic anaemia of pregnancy, responding as it does to folic-acid therapy, also appears to reflect an especially high requirement for folic acid in the rapidly growing maternal and foetal tissues of pregnant women. It has therefore been postulated that chorionepithelioma and related trophoblastic tumours originating in the foetal chorion and initially involving the uterus might prove responsive to treatment with folic-acid antagonists (Li *et al.*, 1956; Hertz *et al.*, 1958).

Treatment of chorionepithelioma and related trophoblastic tumours with methotrexate, with gratifying results in most instances, has been reported in recent years (Li *et al.*, 1956, 1957, 1958; Holland 1958; Hertz *et al.*, 1958; Bagshawe and Brooks, 1959; Buckle, 1959, 1961; Perlson and Whitsitt, 1960; Bagshawe and McDonald, 1960; Manly, 1961; Hreshchysyn *et al.*, 1961; Hamilton, 1962). It is difficult to state the exact number of cases so treated, as some of them may well have been reported on more than one occasion.

Most of the cases of chorionepithelioma in Hong Kong are treated in the Gynaecological Department, University of Hong Kong. From January 1, 1960, to

June 30, 1961, seven cases of chorionepithelioma were treated with methotrexate with very satisfactory results.

### Case 1

A gravida-4 aged 28 was admitted to hospital on January 18, 1960, with a history of seven months' vaginal bleeding following three months' amenorrhoea for which a dilatation and curettage (D. & C.) was done in another hospital one month previously. The uterus was enlarged to the size of a 12-weeks pregnancy and a bluish nodule 5 mm. in diameter was present in the anterior lip of the cervix. The male frog test of the urine was positive up to a dilution of 1 in 200 and radiography of the chest showed several small round opacities scattered over both lungs.

Total hysterectomy, bilateral salpingo-oophorectomy, and right internal iliac artery ligation were done on January 22, after which she developed a productive cough with blood-streaked sputum. On February 16 a bluish nodule about 2.5 cm. in diameter appeared in the anterior vaginal wall 2.5 cm. above the introitus. Another bluish nodule 1.25 cm. in diameter was found in the vestibule just below the external urethral meatus three days later. In the meantime an x-ray film of the chest taken on February 5 (Fig. 1) revealed progressively more extensive involvement of both lungs, and the male frog test, which was negative four days after operation, became positive up to a dilution of 1 in 10. It was decided to treat her with methotrexate, and this was started on February 19, but was discontinued after 50 mg. had been given because of diarrhoea and the presence of blood in the stool. She was found to have amoebiasis, which was treated with emetine and emetine bismuth iodide. Methotrexate was started again a week later. Five subsequent courses of 100 mg. each were given at intervals of two to three weeks. The vaginal and vulval metastases disappeared completely and the male frog test became and remained negative 5 and 10 weeks respectively after beginning methotrexate therapy, and soon afterwards there were hardly any pulmonary metastases in the chest x-ray film (Fig. 2). The notable side-effects were stomatitis, diarrhoea, and alopecia.

After completion of the fifth course her general condition was excellent and she was discharged on May 22 apparently