MALIGNANT TROPHOBLASTIC TUMOURS*

by

K. Bhasker Rao, M.D., D.G.O.

I feel it a great honour done to me for being invited to deliver the 6th Subodh Mitra Memorial Oration this evening. Professor Subodh Mitra was a very distinguished gynaecologist, an eminent educationist, a brilliant teacher and a great organiser, internationally known for his contributions to the surgical management of gynaecological cancer. He was deeply interested in oncology and I may recall the Sir Kedaranath Das Memorial Oration on 'Prevalence of cancer in India and cancer of the cervix' delivered by him in this city 12 years ago (Mitra, 1961). Therefore, I have chosen the malignant trophoblastic tumours as the title for the lecture this evening.

It was only in 1895, Marchand pointed out that choriocarcinoma was completely an epithelial tumour arising from the trophoblast. However, there is still a confusion over what constitutes a malignant trophoblastic neoplasm and there is an urgent need for uniformity in the classification of these tumours so that various centres in different parts of the world could easily compare data regarding their incidence, therapy and results. At present we find the terms metastatic traphoblastic neoplasia, malignant trophoblastic neoplasms, villus and avillus choriocarcinoma, etc. which include invasive moles and other relatively benign trophoblastic lesions under the same category as the notoriously malignant choriocarcinoma.

The incidence of trophoblastic tumours appear to be 2 to 4 times higher in Australia and Latin America compared to North America and Europe (Table I). In Japan, China, South East Asian countries, including India its high incidence has been reported by several workers (Table II). Amongst etiological factors racial, genetic, consanguinity and viral infections have been blamed.

TABLE I

Incidence of Trophoblastic Tumours in Different Countries

Country	Author and Year	Hydatid Mole	Choriocarcinoma
1. U.S.A.	Brewer and Gerbie (1967)	1 in 2093 preg.	1 in 19,734 preg.
2. U.K.	Ian Donald (1964)	1 in 2,000 preg.	—
	Park (1967)	—	1 in 70,000 births
3. Brazil	Fernandes and Marques (1957)	1 in 1,071 preg.	—
4. Mexico	Marquez-Monter et al (1968)	1 in 216 preg.	1 in 2,818 preg.
5. Australia	Steigrad (1969)	1 in 962 preg.	1 in 12,705 preg.

*The Sixth Subodh Mitra Memorial Oration delivered at Calcutta on 1-11-1972 under the auspices of the Bengal Obstetric and Gynaecologist Society.

Received for publication on 18-12-72.

TABLE II

Incidence of Trophoblastic Tumours in South East Asian Countries

Country	Author and Year	Hydatidiform Mole	Choriocarcinoma
1. Indonesia	Djojopranoto et al, (1965)	1 in 90 preg.	1 in 587 Preg.
2. Taiwan	Wei et al, (1963)	1 in 125	1 in 496
3. Philipines	Acosta Sison (1960)	1 in 200	1 in 1,382
4. Japan	Hasegawa (1959)	1 in 232	1 in 271
5. Hongkong	Chen (1962) Chun (1964)	1 in 242	1 in 1,331
6. Singapore	Fox and Tow (1966) Tow (1963)	1 in 689	1 in 5,000
7. Malaya	Llewellyn-Jones (1965)	1 in 342	1 in 3,564
8. Iran	Fakrai (1967)	—	1 in 3,000
9. Iraq	Ghali (1969)	1 in 221	—

Poverty and malnutrition do not appear to be contributory factors. In Singapore, Teoh (1971) reported that even with improvement in socio-economic conditions, the incidence of trophoblastic tumours has remained the same for over a decade. In India, it seems to be more prevalent in the south than in the northern part of the peninsula (Table III). The incidence of choriocarcinoma in our country is variously reported from 1 in 525 (Pai, 1967) in Trivandrum to 1 in 4207 (Chatterjee, 1970), in Calcutta. In the Erskine Hospital, Madurai, during 11 years (1961-1971), 467 trophoblastic tumours were admitted for treatment (Table IV). Of these 398 were hydatidiform moles and 19 were chorioadenoma destruens. There were 50 choriocarcinomas forming 10.7% of all trophoblastic tumours. The hospital incidence of choriocarcinoma was 1 in 1579 pregnancies. However, if all the deliveries in the city are consi-

TABLE III

Incidence of Trophoblastic Tumours in India

City	Author and Year	Hydatidiform Mole	Chorio-carcinoma
1. Delhi	Vohra and Madan (1970)	1 in 409 preg.	1 in 1,808 Preg.
2. Calcutta	Chatterjee (1970)	1 in 589	1 in 4,207
3. Bombay	Daftary et al, (1963)	1 in 505	—
4. Ahmedabad	Mathur and Shah (1964)	1 in 200	1 in 1,200
5. Nagpur	Devi (1959)	—	1 in 6,092
6. Hyderabad	Kanakadurgamba and Rajaram (1970)	1 in 654	1 in 1,000
7. Vizag	S. Rao (1970)	1 in 191	1 in 950
8. Guntur	Sarojini and Reddy (1963)	1 in 296	1 in 748
9. Madras	Rao and Shetty (1961-1962)	1 in 361	1 in 2,958
10. Vellore	Paranjothi (1965)	—	1 in 645
11. Madurai	Rao (1970)	1 in 194	1 in 1,338
12. Trivandrum	Pai (1967)	1 in 160	1 in 525

TABLE IV

Trophoblastic Tumours in Madurai (1961-1971)

	No. of cases	(%)	Incidence	
			Hospital	City
Hydatidiform Mole	398	85.2	1 in 198	1 in 620
Chorio-adenoma destruens	19	4.1	1 in 4,155	1 in 12,998
Choriocarcinoma	50	10.7	1 in 1,579	1 in 4,939
Total	467	100.0	1 in 169	

dered it would be 1 in 4939 deliveries.

The age and parity distribution of choriocarcinoma is shown in Table V.

TABLE V

Age and Parity Distribution of Chorio-Carcinoma

Age	No. of cases	Parity	No. of cases
20 yrs. and below	6	Nullipara	5
21-25 yrs.	13	1	5
26-30 yrs.	9	2	9
31-35 yrs.	8	3	7
36-40 yrs.	8	4	5
40 and over	5	5 +	18
Total	50	Total	50
Range 17-46 Yrs.		Range PO—P10	
Mean Age 29.9 Yrs.		Mean Parity 3.4	

It may be seen at any age from 15-75 years. In our own series the mean age was 29.9 years and the mean parity 3.4. It may be noted that 10% of them were nulliparous women and 36% were grandmultis. The preceding pregnancy was molar only in 38% of our cases (Table VI) compared to 55.8% of 102 choriocarcinomas reported by Hasegawa (1965) in Japan and 82% of 122 cases reviewed by Ratnam *et al*, (1971) from Singapore. Though it mostly follows pregnancy, choriocarcinoma with concurrent intrauterine pregnancy have been reported with secondaries in the vagina, vulva, lungs and brain. (Bulina, 1965; A. Sison, 1965; Saxena *et al*, 1971). Probably, the ectopic choriocarcinoma may be due to malignant transformation of the trophoblastic emboli of a previous pregnancy or even of the

TABLE VI

Preceding Pregnancy in Chorio-carcinoma

	No. of cases	%	Deaths
Hydatidiform mole	19	38	8
Abortion	13	26	9
Full-term delivery	18	36	11
Total	50	100	28

current one. The uterus and extremely rarely the placenta may show evidence of the lesion, the foetus being healthy (McRae, 1951). There are also case reports of choriocarcinoma in the mother and the infant without involving the placenta (Daamen *et al*, 1961). It may rarely follow tubal gestation. When it involves the ovary, it is mostly non-gestational and seen mainly in adolescent girls (Hay and Stewart, 1969). We had one such case. A 15-year-old girl after right ovariotomy in another hospital for a solid ovarian tumour of 15 cm. dm. was admitted 4 weeks later in to our institution with pelvic recurrence. The histological examination of right ovary showed choriocarcinoma. She did not respond to chemotherapy and died a month later.

Pathology: The primary tumour is seen in the uterus which is enlarged to 12-14 weeks' size ofiten with a nodular surface. Bilateral luterin cysts of the ovary are seen in 25-30% of cases. On section, a large vascular growth is seen filling the uterine cavity and penetrating into the myometrium or rarely even to the serosa. Occasionally, it may invade down to the cervix simulating cervical carcinoma or into the broad ligament. In, few cases, the growth may be completely in the myometrium, beyond the reach of the curette. Extremely rarely it might cause inversion of the uterus. (Rao, 1965). In 5 of our cases no primary lesion was seen in the uterus and the growth was seen elsewhere in the vagina, lungs, broad ligament, iliac fossa, etc.

Microscopically, it is characterised by sheets of active hyperchromatic trophoblastic cells of both types (the syncytial and the Langhans) in varying proportions and with absolute loss of villus pattern. There is necrosis of myometrium associated with haemorrhage, leucocytic infiltration and few giant cells

Because of its vary nature, trophoblastic tissue erodes into blood vessels and tumour emboli are carried far and wide to give rise to early metastases in 40-60% of cases. No organ in the body may be spared the favourite sites being lungs, vagina, liver and brain (Table VII). Rarely, the lymph nodes may be involved, as in one of our cases when a patient returned 6 weeks following a panhysterectomy for choriocarcinoma with enlarged superficial left inguinal

TABLE VII

Sites of Secondaries in Chorio-Carcinoma

		Park W. W. and Lees J. C. (1950) Review of 516 cases of Choriocarcinoma	
Lungs	30	*Secondaries:*	
Vagina	19	Lungs	93.8%
Liver	7	Vagina	43.8%
Ovaries	4	Brain	28%
Cervix	3	Kidney	25%
Brain	2	Ovaries	21.9%
Spinal cord	1		
Right iliac fossa	1		
Pouch of Douglas	1		
Sternum	1		
Inguinal lymph nodes	.		
Other sites	4		

glands which were excised and confirmed on microscopic examination as secondaries. Spontaneous regression of proved choriocarcinomatous metastases does not occur after the removal of the primary. The secondary growth here as elsewhere is fully autonomous and independent of the primary and kills the patient in the absence of treatment. The previous claims might have been of metastatic moles and were not well documented (Park and Lees, 1950; Rao and Shetty, 1962; Acosta Sison, 1965).

TABLE VIII

Interval Between Preceding Pregnancy and Symptoms of Chorio-Carcinoma

Interval	Preceding pregnancy		
	Hydatidiform mole	Full-term pregnancy	Abortion
Less than 3/12 months	4 (2)	3 (2)	4 (3)
3- 6 months	7	—	4 (3)
6-12 months	5 (3)	—	3 (3)
1- 3 years	3 (3)	10 (6)	1
3- 5 years	—	3 (1)	1
Over 5 years	—	2 (2)	—
	Total 19 (8)	18 (11)	13 (9)

(Figures in brackets indicate deaths).

The chromosomal studies of trophoblastic tumours have shown that most hydatidiform moles are chromatin positive but depending on the degree of "aberrancy" of the trophoblastic tissue (whether it is chorioadenoma destruens or choriocarcinoma) the chromosomal disturbances vary. These tumours because of intense trophoblastic proliferation produce large amount of HCG which helps in the early diagnosis and follow up of this condition.

Signs and Symptoms: These depend on the site of lesion, whether primary or scondary. Unless alert, a physician may be completely misled, especially when there is no history of preceeding molar pregnancy. The interval between pregnancy and symptoms may vary from 2 weeks to 10 years (Table VIII). Some patients complain of low fever, dyspnoea and haemoptysis suggestive of cor pulmonale or pulmonary tuberculosis. One of our patients had streptomycin therapy for 2 months with a general practitioner prior to her admission. Abdominal pain may also be present. One case was admitted as ileocaecal tuberculosis and 2 others as ectopic gestation. Headache, visual disturbances, coma convulsion and paraplegia may be attributable to intracranial or spinal metastases. Amenorrhoea is seen in some cases when the primary is absent in the uterus.

On examination, most of them are anaemic, the uterus is often enlarged to 12-16 weeks. In 6 of them the os was open and a mistaken diagnosis of incomplete abortion or a submucus myoma was made but an attempt to remove the uterine contents was followed by profuse bleeding. In 3, the cervix showed a growth suggestive of malignancy. The vaginal nodules were seen in 38% of