HUMAN CHORIONIC GONADOTROPIN AS A MARKER IN DETECTION, DIAGNOSIS AND TREATMENT OF TROPHOBLASTIC TUMOURS —AN APPRAISAL

by

JAYASREE ROY CHOWDHURY,* M.B.,B.S., Ph.D., D.Sc., M.A.M.S., M.I.A.C.

and

SUKTA DAS,** M.Sc., Ph.D.

The observation of Otto Warburg (1939) that cancer tissue differentiates itself from normal tissue by marked metabolic changes, initiated a series of studies in search for enzyme markers in the tumour bearing host. The search continues—with respect to their biochemical tumour markers as well, which includes metabolic products, hormones and foetal proteins. Many such products have been valuable indicators of the presence of particular cancerous growth and have facilitated early detection and diagnosis in many cases.

Human chorionic gonadotropin (HCG) —a glycoprotein hormone, originally recognized in the blood and urine of pregnant women (Aschheim and Zondek, 1927) and shown to be produced exclusively by the chorionic villi of placenta (Dickfalusy and Troen, 1961) has been found to be elaborated by essentially all trophoblatic neoplasms (Hertz *et al*, 1961; Dawood *et al*, 1977). The amount of the hormone produced is related to the amount of trophoblastic tissue present (Ross *et al*, 1965). HCG producing trophoblastic tumours include hydatidiform mole, chorioadenoma destruens (invasive mole) and choriocarcinoma, arising from the trophoblast of human pregnancy (Hertz *et al*, 1961). Although of relatively rare occurrence, this group of diseases have received widespread attention due to several unique features viz. (1) these tumours are grafts of malignant foetal chorionic tissue on a maternal host, (2) they invariably produce the protein hormone—HCG, which is directly related to the number of viable tumour cells present and (3) these neoplasms are very sensitive to a variety of chemotherapeutic agents (Hammond and Parker, 1970).

At one time the survival rates for patients with trophoblastic tumours were poor, but with the introduction of chemotherapy followed by improvement in the methodology of treatment and measures to control toxic reactions, the prognosis for a once highly fatal disease have dramatically improved (Hertz *et al*, 1961; Ross *et al*, 1965). Today essentially all patients can be cured. In addition to the improvement in the treatment schedules, the elaboration of HCG by these tumours have assumed immense clinical significance since the detection of this marker hormone could be effectively used as a tool for early detection, diagnosis, prognosis and follow-up of trophoblastic tumours. The presence of this ideal

*Director,

**Junior Scientific Officer,

Chittaranjan National Cancer Reearch Centre, Calcutta.

Accepted for publication on 29-7-82.

tumour marker has obviated the need in many cases for the knowledge of precise histology. This has been particularly useful in the metastatic conditions where treatment could be initiated promptly on the basis of hCG values in sera or urine without operation to determine the histology of the metastatic deposit.

Most pregnancy tests for detection of HCG are positive only when the amount of the hormone present is greater than 500-1000 Iu/lit of urine. They do not extend down to the lower levels of detectability for HCG in patients with trophoblastic diseases (Hertz *et al*, 1961; Curry *et al*, 1975). Assay of serum, plasma or urinary HCG and its subunits by specific radioimmunoassay (RIA) whose sensitivity (less than 5 mIu/ml), allows detection of this hormone at very low levels, forms a superior test for diagnosis, treatment and follow-up of patients where trophoblastic tumour is suspected.

Primary hydatidiform mole is most often diagnosed by detection of vesicular tissue and usually this means a delayed diagnosis. Newer techniques can allow this diagnosis to be achieved at an earlier date. One of the currently recommended techniques is repetitive HCG determination. Repeated assays that fail to show a decline of HCG from a very high level, as would be expected after 80-90 days of normal pregnancy are suggestive of hydatidiform mole (Dawood *et al*, 1977).

The incidence of choriocarcinoma after hydatidiform mole is about 3% and a similar percentage of patients require chemotherapy for invasive mole. The follow-up of mole patients and patients requiring chemotherapy may be determined by routine assay of urinary HCG, based on the following indications:

1. Persistently rising HCG levels—not attributable to new pregnancy.
2. Detectable levels of HCG, 5 months post-evacuation.
3. Persisting high HCG levels, 3-4 weeks after evacuation.
4. Histological evidence of choriocarcinoma with any level of HCG activity.
5. Evidence of pulmonary metastases unless accompanied by persistently falling HCG titres.

This scheme has been highly successful in early diagnosis and prompt and effective therapy (Bagshawe, 1969).

Apart from follow-up after mole, HCG measurements play an important part in the diagnosis of choriocarcinoma arising after term delivery on non-mole abortion. In these cases, disease suspected by clinical, radiological and histological examination can be confirmed by the presence of HCG. A diagnosis of choriocarcinoma is untenable if HCG is not detectable by RIA (Bagshawe, 1978). It has been possible to detect gestational choriocarcinoma in non-pregnant patients with no evident clinical disease on the basis of HCG determination alone.

The value of HCG concentration in serum or urine has substantial prognostic implications. In general, the high HCG values indicate poor prognosis (Bagshawe, 1976).

In general, both surgery and irradiation for malignant trophoblastic disease have not been found to be totally satisfactory. Greene (1959) had reported of a 15% mortality in patients with invasive mole treated by surgery alone. The surgical treatment in choriocarcinoma is even less rewarding as a primary therapeutic modality (Brewer *et al*, 1961).

Chemotherapy is very effective in this group of diseases as documented in numerous reports. Good response to these tumours to a variety of systematically administered chemotherapeutic agents in-

cluding methotrexate, actinomycin D, vinca alkaloids and 6-mercaptopurine have been reported. In case where patients did not respond to a single-agent chemotherapy combination chemotherapy and arterial infused chemotherapy have been suggested (Hammond *et al*, 1973 and Maroulis *et al*, 1975).

It has become a practice to monitor plasma or urinary HCG levels for therapeutic supervision of all trophoblastic tumours. Serial measurement of HCG during chemotherapy usually gives a good indication of the response to the drugs. With successful course of treatment, a gradual and progressive fall in the HCG titre can be noted, whereas failure of HCG values to fall after a course of treatment or an initial fall followed by a rise to near pre-treatment values indicated drug resistance (Bagshawe, 1978). Thus HCG determination allowed clinicians to select a course of treatment or change to a more effective chemotherapeutic agent without delay.

A close follow-up is usually essential for sometime after discontinuation of chemotherapy. Serial HCG assay have been helpful in this aspect too. The diagnosis of remission is made only after few consecutive HCG titre show normal values (Tomoda *et al*, 1977). Recurrence can also be detected by the reappearance of HCG in sera or urine. It may be recommended that HCG assays be performed at two week intervals during the first 3 months after termination of treatment followed by one-monthly or bimonthly check-ups during the next two years.

Since the role of HCG as marker in trophoblastic tumours became universally recognized and accepted, many investigators set upon exploring possibilities for HCG as marker in non-trophoblastic tumours. Reports from different laboratories, including our own, have clearly indicated that many non-trophoblastic tumours also secrete HCG which are detectable by specific RIA. The malignant tumours which elaborated HCG and released it in circulation are mainly those of cervix, breast, ovary, stomach, liver and pancreas (Bagshawe *et al*, 1978; Das *et al*, 1981). Our studies reveal that HCG positive cases of cancer of the uterine cervix is highest (around 65%, the HCG values increasing progressively with the disease. It would be worthwhile to assay the HCG titres during the course of treatment as well. A survey of literature shows that serum HCG levels have proved useful for prediction of response to treatment and detect recurrence of many malignant tumours viz. prostatic carcinoma (Broder *et al*, 1977), metastatic breast carcinoma (Tormey *et al*, 1977), large cell carcinoma of the lung (Kikuoka *et al*, 1980) and intracranial germ cell tumours (Arita *et al*, 1980). These reports suggest that HCG has future prospect as marker for monitoring treatment in non-trophoblastic malignant tumour as well.

References

1. Arita, N., Ushio, Y. Hayakawa, T., Uozumi, T., Watanabe, M., Mori, T. and Mogami, H.: Oncodevelopmental. Biol. Med. 1: 235, 1980.
2. Ashheim, S. and Zondek, B., Klin Wschr. 6: 1322, 1927.
3. Bagshawe, K. D.ff "Choriocarcinoma—The clinical biologl of trophoblast", London, 1969, Arnold.
4. Bagshawe, K. D.: Cancer, 38: 1373, 1976.
5. Bagshawe, K. D.: in "tumour Markers —Determination and Clinical Role" ed. K. Griffiths, A. M. Neville and C. G. Pierrepoint, Cardiff, 1978. Alpha-Omega Publ. Ltd. p. 90.
6. Bagshawe, K. D., Lequin, R. M., Sizaret, P. H. and Tatarinov, Y. S., Europ. J.: Cancer. 14: 1331, 1978.
7. Braunstein, G. D., Vaitukaitis, J. L.

Carbone, P. P. and Ross, G. T. Ann. Int. Med. **78:** 39, 1973.

8. Brewer, J. I., Rinehart, J. J. and Dunbar, R.: Am. J. Obstet. Gynaec. **81:** 574, 1961.
9. Broder, L. E., Weintraub, B. D., Rosen, S. W., Cohen, M. H. and Tejada, F.: Cancer. **40:** 211, 1977.
10. Curry, S. L., Hammond, C. B., Tyrey, L., Creasman, W. T. and Parker, R. T.: Obstet. Gynaec. **45:** 1, 1975.
11. Das, S., Bhattacharya, S. and Roy Chowdhury, J.: Ind. J. Med. Res. **74:** 904, 1981.
12. Dawood, M. Y., Saxena, B. B. and Landesman, R. Obstet. Gynaec. **50:** 172, 1977.
13. Dickfalusy, E. and Troen, P., Vitamins and Hormones, **11:** 230, 1961.
14. Greene, R. R.: Ann. N. Y. Acad, Sci. **80:** 143, 1959.
15. Hammond, C. B., Borchert, L. G., Tyrey, L., Creasman, W. T. and Parker, R. T. Amer. J. Obset. Gynaec. **115:** 4, 1973.
16. Hammond, C. B. and Parker, R. T., Obstet. Gynaec., **35:** 132, 1970.
17. Hertz, R., Lewis, J. Jr. and Lipsett, M. B.: Am. J. Obste. Gynaec. **82:** 631, 1961.
18. Kikuoka, H., Ueda, Y., Emoto, M., Miyamura, K., Okada, K., Tagami, Y. and Okada, N.: Wakayama Med. Rep 22: 137 1980.
19. Maroulis, G. B., Hammond, C. B., Johnsrude, I. S., Weed, J. C. Jr. and Parker, R. T.: Obstet. Gynaec. **45:** 397, 1975.
20. Ross, G. T., Goldstein, D. P., Hertz, R., Lipsett, M. B. and Odell, W. D.: Am. J. Obstet. Gynaec. **93:** 223, 1965.
21. Tomoda, Y., Asai, Y. and Arii, Y.: Cancer, **40:** 1016, 1977.
22. Tormey, D. C., Waalkes, T. P., Simon, R. M.: **29:** 2391, 1977.