Secretion of hypothalamic and pituitary hormones by non-endocrine tumours

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That non-endocrine cancers can produce clinical syndromes of apparent hormone excess has been known for some time (Rees and Ratcliffe, 1974). Now there is ample clinical and biochemical evidence that many polypeptide hormones may be produced and released by human tumours which originate in tissues which are not normally regarded as sites for the physiological production of the hormones. In some instances—for example, inappropriate production by a cancer of adrenocorticotrophic hormone—that syndrome may be clinically obvious. Thus Cushing's syndrome in a patient with a relatively slowly growing lung cancer or carcinoid will be obvious. More commonly with ectopic ACTH production, however, the full clinical picture of Cushing's syndrome is not apparent—rather there is pronounced muscle weakness, hypokalaemic alkalosis, pigmentation, and very high levels of plasma cortisol and ACTH.

Most of the ectopic humoral syndromes are diagnosed on the clinical and biochemical improvement after tumour resection, on finding high plasma and tumour extract concentrations of hormones, in some patients on localisation of hormones in tumour cells by immunofluorescence, and on the presence of an arteriovenous gradient of hormone concentration across the tumour. There are now many instances of cultured cancer cells being shown to release hormone into the culture medium. In a few cases the biosynthesis of hormone has been demonstrated by the incorporation of radioactive amino-acids into the peptide.

Although most research in this area has been concentrated on the study of hormone production, presumably because hormones readily manifest their presence, other polypeptides also are produced and released by tumours in greater quantities than would be expected from the tissue of origin. These include enzymes such as alkaline phosphatase (Nathanson and Fishman, 1971), lysozyme (Kovanyi and Letnansky, 1971), amylase (Amman *et al.*, 1972), and plasminogen activator (Davidson *et al.*, 1969) as well as a variety of fetal proteins that are normally present

in plasma only in small quantities during adult life (Alexander, 1972), such as carcinoembryonic antigen (Gold, 1970) and alpha fetoprotein (Abelev, 1971).

Cellular mechanisms

The cellular mechanisms by which cancers produce ectopic hormone are not understood. There are various possibilities.

(1) Entrapment of circulating hormones by tumour capable of binding them has been discussed for some years. There is no evidence to support this and it seems unlikely.

(2) The neoplastic cells may have a disorder of mechanism for polypeptide synthesis so that random production of polypeptide chains results. Some of the polypeptides may have biological or immunological properties that resemble known hormones. If this theory were correct the production of a recognisable polypeptide would be unusual, which is not the case, and the particular polypeptide produced would account for only a small fraction of the cell output.

(3) Polypeptide production may originate from material within a tumour-virus genome. There is evidence in vertebrates that somatic cells may contain the genetic information for producing tumour viruses in an unexpressed form (Todaro and Huebner, 1972). Alternatively, if tumours are a result of new viral infections the new genetic material could be acquired during infection and tumour induction.

(4) There is a general body of evidence that the hormonal peptides from cancers are very similar to or identical with known hormones or their precursors, which suggests that part of the genetic code is being appropriately transcribed and translated. In this is indeed confirmed two general theories may account for ectopic hormone production.

(a) Pluripotentiality. If all adult cells contain all the genetic material that is needed to synthesise all the proteins which can be produced by the organism the production of an ectopic hormone may result from genetic derepression taking place during cancer development.

(b) An alternative theory is that these particular tumours arise only from specialised cells within tissues (Cohnheim, 1889) and that the properties of these cells may include the capacity to produce polypeptides. The production of hormones becomes apparent when the mass of these cells increases. The modern development of Cohnheim's 'cell rest' hypothesis is that certain cells of the adult gastrointestinal tract, pancreas, thyroid, and pituitary share morphological and histochemical properties (Pearse, 1968) and have a common embryological origin from the neural crest (Pearse and Carvalheira, 1967; Pearse and Polak, 1971). When these cells become neoplastic or hyperplastic they retain the histochemical and ultrastructural characteristics of the group (Elias *et al.*, 1972; Pearse and Polak, 1974). Multiple hormone production by such tumours (Law *et al.*, 1965) or the production of another hormone which is usually produced by another cell of the series (Donahower *et al.*, 1968) may be explained by this common origin.

Of all these theories 4(a) and (b) are now the most popular, although either alone does not seem sufficient to explain the phenomenon. Any conclusions about the mechanisms of ectopic hormone production need to be based on careful clinical studies, since very little experimental evidence is available. Considerable information has been obtained from studies of patients with cancers producing 'pituitary' hormones.

ACTH

Although the syndrome occurs most commonly with oat cell carcinoma of the bronchus there have been a number of well documented cases associated with other cancers—particularly thymoma, bronchial carcinoid, medullary carcinoma of the thyroid, and islet cell carcinoma of the pancreas. This grouping of tumours favours the possibility that the tumour cells arise from a common embryological origin, or that the nature of the 'derepression' that takes place with these cancers may be such that the cellular genetic material coding for ACTH synthesis is reproducibly exposed. Thus theory 4(a) or 4(b) above might apply, or a combination of the two. This syndrome has been studied experimentally by Gewirtz and Yalow (1974), who obtained evidence of immunoreactive ACTH in extracts of lung tissue from smoking dogs.

The observation that immunoreactivity is often greater than bioactivity in tumour extracts (Rees and Ratcliffe, 1974) is important in deciding whether 'tumour' ACTH differs from 'pituitary' ACTH. Ratcliffe *et al.* (1972) and Orth *et al.* (1973) have evidence that tumours contain fragments of the ACTH molecule and, as expected, these are recog-

nised to differing degrees by different antisera. It would also be expected that only some of the fragments would be biologically active. Gewirtz and Yalow (1974) have noted in plasma and in extracts of tumour from patients with the syndrome the presence of a high molecular weight form of ACTH ('big' ACTH) which can be converted to the same size as ACTH by mild trypsin treatment. Big ACTH was not found in plasma of patients with Addison's disease. Possibly this large molecule is a biosynthetic precursor of ACTH, but a precursor-product relationship has not been shown.

None of these observations excludes the possibility that the tumours are synthesising authentic ACTH, identical with the pituitary form. The persistence of a possible precursor and the generation of fragments could be explained by the absence from the tumour cells of the normal packaging and secretory mechanisms.

Clinically, the syndrome may be easy to recognise in those patients with relatively slowly growing tumours, and since the high steroid output contributes to the illness surgical removal of the tumour has been successful (Orth and Liddle, 1971). Treatment with metyrapone may be useful. A thymoma has been localised preoperatively by multiple venous sampling for ACTH assay and been successfully treated by surgery (Lowry *et al.*, 1977). ACTH assay may be used in such patients to detect tumour recurrence.

Growth hormone

Fried (1943) noted the similarity between acromegaly and chronic hypertrophic pulmonary osteoarthropathy (HPOA). He thought that dyspituitarism was a possible cause of the latter syndrome. Steiner *et al.* (1968) and Dupont *et al.* (1970) reported that some patients with bronchogenic carcinoma and HPOA had raised growth hormone levels, but this metabolic abnormality is not invariably a feature of patients with HPOA (Cameron *et al.*, 1969; Beck and Burger, 1972). Significant amounts of growth hormone have been found in bronchial carcinomas by several groups, and Beck and Burger (1972) have reported quite high levels in extracts of gastric carcinomas. Greenberg *et al.* (1972) have demonstrated synthesis of growth hormone by a lung tumour in cell culture.

The conclusion from these various studies is that tumour production of growth hormone can occur, that it is unlikely to be related to HPOA, and that no metabolic complication need be apparent. Clinically evident carbohydrate intolerance has not been reported, but failure of suppression of growth hormone during the glucose tolerance test has been described (Burger *et al.*, 1970; Sparagana *et al.*, 1971).

Antidiuretic hormone

Inappropriate production of antidiuretic hormone (ADH) with water retention and hyponatraemia has been recognised for some time in patients with oat cell carcinoma of the bronchus. Radioimmunoassay of ADH continues to present difficulties, but in studies carried out by a number of groups the tumour ADH closely resembles arginine vasopressin by chemical, immunological, and biological criteria (Barraclough *et al.*, 1966). George *et al.* (1972) demonstrated the synthesis of vasopressin by a cancer in vitro by incubating tumour slices from a lung carcinoma, and Martin *et al.* (1972) found ADH activity released by cultured cells from a patient with inappropriate ADH production. In the latter experiments the ADH in serum, ascitic fluid, and culture medium was associated non-covalently with a larger protein. Hamilton *et al.* (1972) made a similar observation and, further, suggested that tumours might be producing neurophysin as well. If this is so it indicates that the tumour very closely reproduces the normal biosynthesis of ADH. If neurophysin production does occur it provides an example of production of a 'hormone' which would not be evident clinically, since no biological effects of neurophysin are known.

Other pituitary hormones

Galactorrhoea as a result of ectopic prolactin production is recognised, and Turkington (1971) used cell culture to show release of biologically active prolactin into the medium by cells from a bronchogenic carcinoma and from a renal cell carcinoma associated with galactorrhoea. There are many reports of gonadotrophin production by cancers. If those tumours showing trophoblastic differentiation are excluded the condition has presented most commonly as gynaecomastia and galactorrhoea in patients with carcinoma of the bronchus (Fusco and Rosen, 1966) or as precocious puberty in young males with liver tumours (McArthur *et al.*, 1973). The problems of precisely identifying the hormone produced is compounded in the case of the gonadotrophic hormones by the cross-reactivity of antisera and by the possibility of separate release of α and β subunits of the hormones. Tashjian *et al.* (1973) have shown dissociated release of the subunits of HCG in a cloned cell line from a bronchogenic carcinoma.

Hypothalamic hormones

If tumours are capable of producing hormones probably they might be shown to produce any of the

range of 'releasing hormones', but very little information is available. Upton and Amatruda (1971) found evidence of corticotrophin-releasing activity in extracts from two primary cancers and from the metastases of one of them. Corticotrophin-releasing activity was evident in vivo and in vitro. This activity cannot be compared with the corresponding hypothalamic activity since neither agent has been isolated. The same can be said of the experiments of Beck *et al.* (1973), who found growth hormone-releasing activity in extracts of human cancers assayed by stimulating growth hormone release from superfused rat pituitaries in vitro.

Since the discovery of the growth hormone release-inhibiting hormone (somatostatin) (Brazau *et al.*, 1973) there has been some uncertainty whether a specific hypothalamic hormone stimulating growth hormone release exists, although there have been many experiments showing this property in hypothalamic extracts (Krulich *et al.*, 1968; Schally *et al.*, 1969; Beck *et al.*, 1973). Even if no specific hypothalamic factor exists, however, there may be other substances capable of stimulating pituitary growth hormone release and thereby cause the abnormalities known to occur in some patients with cancer (Sparagana *et al.*, 1971). High plasma growth hormone levels and failure of suppression after glucose have been found in eight out of 18 patients with bronchial carcinoid tumours (Feldman *et al.*, 1975). The fact that in this series the abnormality of growth hormone seemed unrelated to excess serotonin production raised the possibility that carcinoid tumours produce some other factor promoting growth hormone release.

The best evidence that tumours can produce hypothalamic hormones has been obtained recently by Jeffcoate *et al.* (1977) in a patient with a thymoma producing not only ACTH with Cushing's syndrome but also somatostatin and LH-RH, both readily measured by radioimmunoassay and showing, when diluted, a curve parallel to that of standards.

Conclusion

The difficulties in diagnosing and recognising the syndromes due to ectopic pituitary hormones are considerable, and a new dimension has been added with the discovery of the hypothalamic hormones. If as seems likely, cancers can also produce these, and perhaps also other brain peptides, research in this area will certainly be difficult. But there are most remarkable possibilities for determining the clinical metabolic effects of cancers and discovering causes for the many humoral manifestations of malignant disease.

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