Cancer and Ectopic Hormones

W. P. U. JACKSON

SUMMARY

Tumours of non-endocrine organs may cause endocrine syndromes through the production of 'ectopic' hormones. Ectopic corticotrophin was probably responsible for the first published cases, and the clinical condition related to this hormone is described. It can be mimicked by ectopically-produced corticotrophin-releasing hormone.

Tumorous hypercalcaemia is usually caused by an ectopic parathyroid hormone-like substance, while inappropriate antidiuresis may be due to an ectopic antidiuretic hormone. Hyperthyroidism can be induced by a thyroid-stimulating hormone derived from trophoblastic tumours, which probably differs from normal placental TSH.

The possible mechanisms underlying these phenomena are 'de-repression' (most likely) and total breakdown of the genetic code in the tumour cells.

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Cancer can do many strange things. Tumours of non-endocrine organs may cause endocrine syndromes, due to the cancer cells assuming the ability to synthesise polypeptides that are either identical with normal hormones or can exactly mimic their effects. These are the 'ectopic' hormones.

What follows is no exhaustive review of the situation,[1-3] but rather an attempt to highlight some of the conditions that may be of particular interest to surgeons and others.

Ectopic Corticotrophin (ACTH) Production[4]

In 1928 Brown[5] described the condition he called 'diabetes of bearded women', in association with oat-cell carcinoma of the bronchus, and in 1931 Leyton and co-workers[6] described 2 cases of Cushing's syndrome with epithelial tumours of the thymus, but the relationship between tumour and syndrome remained obscure for many years. Cushing himself did not describe his own syndrome until 1932.

The main tumours responsible for ectopic ACTH production are: bronchus (oat-cell); carcinoid of gastrointestinal tract and bronchus; thymus (epithelial cell?); thyroid (medullary carcinoma); pancreatic islets; phaeochromocytoma; also parotid, parathyroid, stomach, gall bladder, kidney, colon, prostate, ovary, testis, breast, trachea.

It has been suggested[5] that all ACTH-producing cells share certain common histochemical, cytological and ultrastructural properties and may even have a common embryological origin—the neural crest.

Unlike primary Cushing's disease, the ectopic ACTH syndrome is more common among males and presents with muscular weakness and wasting with marked hypokalaemic alkalosis, rather than the typical appearance of Cushing's syndrome. Hyperglycaemia, oedema and pigmentation are frequent, the latter being due to concomitant ectopic production of beta-MSH, a closely related polypeptide. Deterioration is rapid, but successful treatment of the tumour has led to remission of the hypercorticism.

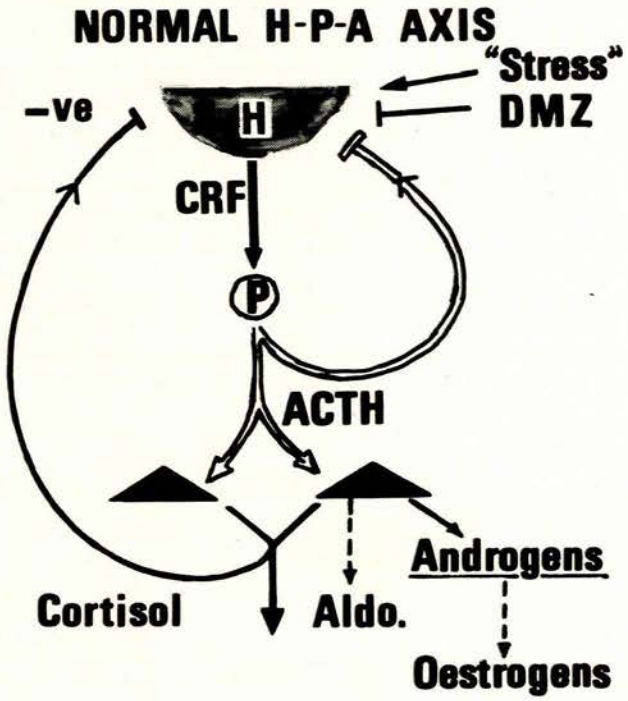

Fig. 1. Normal hypothalamic-pituitary-adrenal axis. See text.

The normal hypothalamic-pituitary-adrenal axis is depicted in Fig. 1. The hypothalamus secretes the corticotrophin-releasing hormone (or factor) (CRH or CRF) which stimulates the pituitary to release ACTH, which in turn initiates the chemical pathway in the adrenals leading to formation of cortisol and other steroids. Cortisol controls the feedback mechanism by inhibiting the hypothalamic production of CRH and so indirectly controls its own levels. Synthetic corticosteroids (e.g. dexamethasone, DMZ) will also inhibit CRH and ACTH production, while 'stress' situations stimulate them.

With ectopic hormone formation, large amounts of ACTH-like substances are produced which give rise to

Groote Schuur Hospital and Department of Medicine, University of Cape Town
W. P. U. JACKSON, M.A., M.D., F.R.C.P., F.R.S. (S.A.)

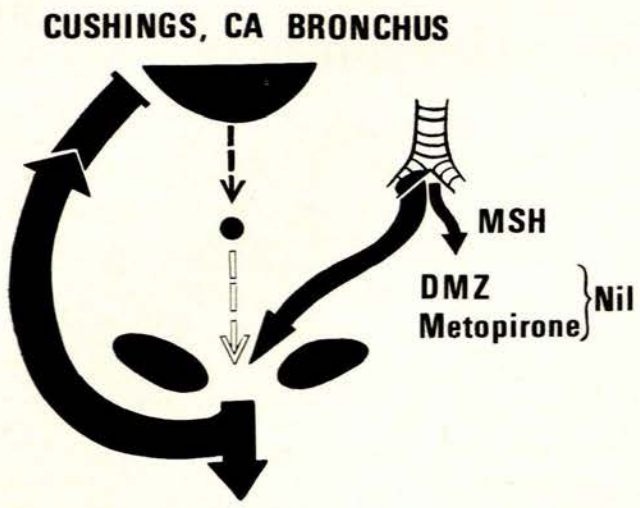

Fig. 2. Cancer of bronchus producing ACTH-like substance and MSH. Adrenal hyperplasia, massive amounts of cortisol, pituitary suppression. No effect of dexamethasone or metyrapone.

bilateral adrenal hyperplasia and tremendous overproduction of cortisol, which cannot be suppressed by dexamethasone (Fig. 2).

The hypothalamic-releasing hormones are also simple polypeptides, so it is not surprising that CRH-like substances can also be produced by cancer cells, leading to the same clinical syndrome, but now with ectopically-provoked overactivity of the pituitary and overproduction of normal pituitary ACTH (Fig. 3). Tumours responsible have arisen in the bronchus[9] and pancreas. In this situation the cortisol production may be responsive to dexamethasone and metyrapone.

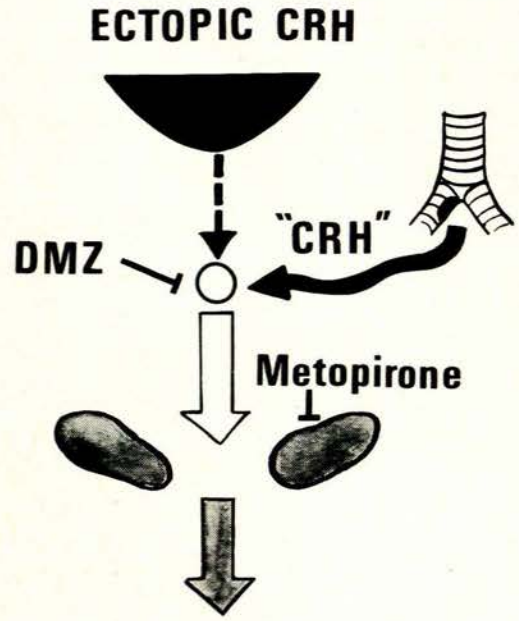

Fig. 3. Cancer of bronchus producing CRH. The patient's own pituitary gland now releases excessive ACTH. See text.

Hypercalcaemia, Ectopic PTH-Like Hormone[10]

Hypercalcaemia in relation to tumours is most common in cases of breast cancer with bony metastases and here it is presumably caused by simple dissolution of bone salt (Fig. 4). In this condition one would logically expect the serum phosphorus to be high, since this element is also driven into the bloodstream from the skeleton, and indeed it usually is; but not always, as we shall see.

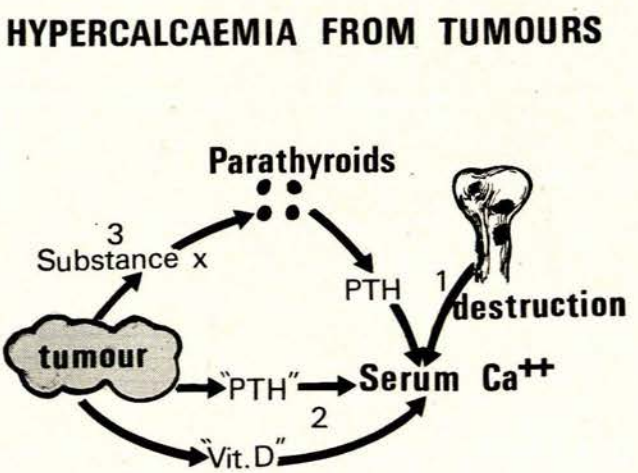

Fig. 4. Theoretical possibilities include: (*i*) bone destruction by metastases; (*ii*) production of PTH and vitamin D-like substances by tumour; (*iii*) production of parathyroid-stimulating substance.

In the case of other tumours the serum calcium level may be raised without any direct skeletal involvement. Here the serum phosphorus level is usually low and the syndrome is due to an ectopic parathyroid hormone-like hormone. Tumours responsible are: bronchus (squamous-cell)—most commonly; kidney—next commonest; pancreas, parotid, adrenals, hepatoma, colon, spleen, penis, lymphoma, leukaemia, sarcoma, breast (one single case, with secondaries in liver).

Ectopic hormone hypercalcaemia may be difficult to distinguish from primary hyperparathyroidism. It is common in males who are clinically ill with a short history and without either stones or bone disease. The serum calcium level may be very high. The alkaline phosphatase may be raised in some cases without bone involvement, which does not happen in hyperparathyroidism. In some cases the hypercalcaemia responds to cortisone. The two conditions may coexist.

Inappropriate Antidiuretic Hormone[11]

The syndrome of inappropriate antidiuresis, due to ectopic ADH, occurs most commonly with bronchial carcinoma (oat-cell), and has also been reported in cases of cerebellar haemangioblastoma, pituitary chromophobe adenoma, pancreatic neoplasm, lymphoma and duodenal tumour.

Clinically, overhydration leads to somnolence, irritability, confusion and disorientation. Dilutional hyponatraemia is present with low serum sodium and chloride levels together with a concentrated urine. The plasma volume is normal or raised and the haematocrit normal or low. Glomerular filtration rate and adrenal function are normal (otherwise the diagnosis is extremely difficult).

The mechanism of production of this syndrome is incompletely understood. ADH increases distal tubular reabsorption of water, leading to water retention which increases the circulating blood volume and this causes simple dilutional hyponatraemia. One might expect the hyponatraemia to stimulate aldosterone release with consequent oedema, but this does not occur. The logical treatment is therefore restriction of fluid intake.

Hyperthyroidism, TSH Production[12]

The tumours involved are trophoblastic—choriocarcinoma and hydatidiform mole; also carcinoma (embryoma) of testis; it is doubtful whether tumours at any other site have been responsible for hyperthyroidism,[12] though some (e.g. bronchus) may be capable of producing a TSH.

Clinically there are no eye signs, perhaps because there is no excess of the long-acting thyroid stimulator (LATS), and little or no goitre. The usual thyroid function tests are similar to those in Grave's disease, but complete remission occurs on control of the primary tumour.

The hormone production in this syndrome should not, strictly speaking, be called 'ectopic', because the normal placenta produces TSH. The two polypeptides are, however, not identical, tumour TSH being a larger molecule with immunological differences. It may represent a specific fetal protein.

Other syndromes related to ectopic hormone production include:

'Typical' carcinoid syndrome (5-hydroxytryptamine = serotonin)—midgut tumours.

'Atypical' carcinoid syndrome (5-hydroxytryptophan + histamine)—foregut derivatives (e.g. bronchus).

Erythrocytosis (erythropoietin)—cerebellar haemangioblastoma, hepatoma, etc.

Precocious puberty in boys (gonadotrophins LH or HCG)—bronchus (large cell), hepatoma.

Gynaecomastia (LH)—teratoma, bronchus.

Galactorrhoea (prolactin)—bronchus (undifferentiated), kidney.

Galactorrhoea (placental lactogen = somatomammotrophin)—gonadal and trophoblastic tumours.

MECHANISM

Why and how do cancer cells start producing hormones of another tissue? It is believed that the DNA of all primitive cell nuclei is totipotential—capable of producing any natural polypeptide sequence—but that during tissue development this generalised genetic-biochemical information is repressed by histones, so limiting the adult cell to just doing its own thing. Malignant transformation, itself a genetic abnormality, is imagined as de-repressing this information, so allowing the cancer cell to synthesise other proteins. On this theory the ectopically produced hormone should be identical with the normal hormone, and indeed this usually appears to be the case. Further, non-protein hormone production would be unlikely since this would require extremely massive de-repression in order for all the required enzymes to be produced.

Another hypothesis suggests that regulation of the genetic code is totally lost, the cancer cell fires away in all directions, indiscriminately producing vast series of polypeptides, some of which, by laws of chance, have biological consequences. This theory does not seem to fit with the apparent tumour specificity, for instance in that the bronchial squamous-cell carcinoma is associated with hypercalcaemia, whereas the oat-cell tumour is responsible for almost all other ectopic hormones.

One may wonder whether other peptides, at present unknown, may cause some of the other systemic manifestations of cancer—neurological, dermatological, haematological, skeletal, vascular, renal—the fever, anaemia and even death.

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