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EDITORIAL *VAN DIE REDAKSIE*

Recent Advances in Endocrinology

In this issue of the *Journal* we publish some of the papers presented at an Interdisciplinary Meeting on Recent Advances in Endocrinology, which was held on 17 March 1973, at Groote Schuur Hospital, Cape Town, under the Chairmanship of Professor J. H. Louw.

The four guest editorials in this issue, by Professor Jackson, and Drs Vinik, Pimstone and Epstein, were specially written to relate to the articles and should be read in conjunction with these.

In order to ensure that the articles would indeed incorporate the most recent advances in the field of endocrinology, and because of the lapse of time between the presentation of the original papers and publication, all the material included in this issue was submitted to the various authors for revision and addition during November 1973.

Ectopic Production of Hormones by Non-endocrine Tumours

Modern techniques of hormone assay—especially radio-immunoassay—have led to a clearer understanding of many bizarre syndromes connected with cancers. Cancer cells have been shown to be able to synthesise polypeptides identical with or closely resembling almost all known peptide hormones, and can thus mimic the known 'too-much' endocrine syndromes and even produce a few new ones. Hormones produced by tumours of non-endocrine organs are known as 'ectopic'. Obviously, not all tumoral hormone production is ectopic, for example insulin from an insulinoma, calcitonin from a thyroid medullary cell carcinoma, gastrin from the delta cells of the pancreatic islets in the Zollinger-Ellison syndrome. The TSH production by trophoblastic neoplasms is also, strictly speaking, not ectopic, as admitted by Jackson in his review in this issue (see page 347).

Immunoassay has led to the discovery that such ectopic hormone production is common, but frequently unaccompanied by any evident clinical manifestations. Thus an alpha cell tumour of the pancreatic islets produced not only glucagon, its proper hormone, but also gastrin, corticotrophin, and melanocyte-stimulating, antidiuretic, and parathyroid hormones. On the other hand, hypoglycaemia, associated particularly with large mesenchymal tumours and hepatoma, has never clearly been shown to be caused by overproduction of insulin.

Two cases of interest have recently been reported from Groote Schuur Hospital. The first was that of a 30-year-old man presenting with Cushing's syndrome, for which he underwent bilateral total adrenalectomy.[1] One year later a thymoma was discovered, which had rapidly enlarged. The removed tumour contained large amounts of ACTH (by radio-immunoassay) and secretory granules were demonstrated by electron microscopy. The second case was a 50-year-old man who presented with the syndrome of excessive secretion of antidiuretic hor-

mone (ADH) together with clinical and biochemical hypopituitarism.[2] At autopsy a bronchogenic oat-cell carcinoma was found with metastases to the hypothalamus and pituitary gland. Neurosecretory granules were seen in the tumour on electron microscopy, and immunoassay demonstrated that it contained large amounts of ADH, which was apparently identical with the naturally-occurring arginine vasopressin.

Many tumours are specific with regard to their ectopic endocrine activities. Thus the ectopic hyperparathyroid syndrome occurs with squamous cell bronchial carcinoma, whereas most other endocrine disorders associated with bronchial neoplasms occur with the less common oat-cell tumour. Hepatoma is particularly related to precocious puberty in boys (gonadotrophins), erythrocytosis (erythropoietin) and hypoglycaemia (unknown mechanisms). Certain diagnostic implications may arise. For instance the discovery of hypokalaemic alkalosis or of dilutional hyponatraemia should suggest the presence of an oat-cell bronchial neoplasm even without any confirmatory radiological evidence. Gynaecomastia with a pulmonary lesion suggests an LH-producing tumour. A neat negative inference sometimes occurs in cases of breast carcinoma. In this condition any hypercalcaemia is not due to ectopic parathyroid hormone but to actual skeletal replacement, and consequently the serum phosphate is also raised. Hence in cases with low serum phosphate, true primary hyperparathyroidism is usually present as a coincidental disease.

Clubbing of the fingers and toes and the more striking hypertrophic osteo-arthropathy are associated with lung tumours and may regress rapidly if the primary growth can be removed. Ectopic growth hormone production by the tumour has been postulated as the cause, but this cannot be considered proved. Many other unexplained phenomena can accompany cancer. These include myopathies, neuropathies, encephalopathy, myelopathy; acanthosis nigricans, ichthyosis, dermatomyositis, dermatitis herpetiformis, vascular thromboses, leukaemoid and leuco-erythroblastic reactions, red cell aplasia, eosinophilia; proteinopathies and amyloidosis and nephrotic syndrome. It is quite likely that as yet unrecognised polypeptides, or perhaps other chemical agents, produced by the primary tumour, will be found to be responsible for many of these complications of cancer. It is also possible that cancers produce further chemical substances, which may be polypeptides, that impair the functions of normal body tissues and lead to the anaemia and cachexia of the victim, and even to his death, the precise mechanism of which is not revealed by an autopsy at which the vital organs appear substantially undamaged.

W. P. U. JACKSON

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The Entero-Insular Axis

As early as 1902 Moore and colleagues[1] demonstrated a blood sugar-lowering effect of acid alcohol extracts of dog duodenum. Fifty years later it was shown that glucose disappeared more rapidly from blood when given orally than when a comparable dose was given intravenously. This phenomenon was shown to be insulin-mediated, and a gut insulinotrophic hormone 'incretin' postulated.

Several gut hormones are contenders for this title, since all have been shown to release insulin *in vitro*. These include gastrin, secretin, cholecystokinin-pancreozymin (CCK-PZ) gut glucagon, and two recently discovered hormones, gastro-intestinal inhibitory peptide (GIP) and vaso-active intestinal polypeptide (VIP). Controversy still exists as to which, if any, of these hormones fulfil the role of 'incretin',[2] but undoubtedly a hormone, or group of hormones, produced in the gut, are insulinotrophic.

Glucose stimulates insulin release from several postulated functional pools in the pancreas, and it seems that gut hormones can stimulate insulin secretion from the acute release pool, as well as from a defined glucose-independent source. Thus in diabetics whose pancreases are unresponsive to glucose, gut hormones may nevertheless stimulate insulin secretion.

The hypothetical role of these gut insulinotrophes would then be to minimise fluctuations in blood

glucose following a meal by anticipating the arrival of metabolic substrates in the blood, and evening out large swings in blood glucose levels. Further, since CCK-PZ, primarily released after mixed fat and protein meals, also stimulates glucagon release, it appears suited to re-direct body metabolism towards protein storage by increasing insulin secretion and providing alternative energy substrate in the form of glucose derived from glucagon-stimulated glycogenolysis.

Maturity onset diabetics in whom insulin resistance, rather than insulin deficiency, results in glucose intolerance, demonstrate excessive early insulin responses to oral glucose. Thus, overactivity of the entero-insular axis due to primary hypersecretion of gut hormones may be the earliest lesion in diabetics, and the fault lies in the gut and not in the pancreas at all!

That an exaggerated fall in blood glucose following a meal, referred to as reactive hypoglycaemia, is not due to insulin oversecretion is now fairly well accepted. It appears instead that there is oversecretion in sensitive individuals of gut glucagon which is devoid of glycogenolytic activity, but competes with pancreatic glucagon for receptors in the liver, thus antagonising the glycogenolytic action of the latter and permitting unopposed insulin action, causing an excessive fall in blood glucose concentration.

Lastly, an oral phase of insulin secretion has been shown in dogs which may be neurally or neurohormonally mediated. Hence, it may not only be excessive food intake which after digestion leads to obesity, hyperinsulinism and diabetes, but also that which is contemplated or enters the mouth. The postulated sequence would thus be oversecretion of insulin, increasing fat stores resulting in obesity, insulin resistance and diabetes.

A. I. VINIK

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FSH/LH-RF

It is almost forty years since Popa and Fielding[1] demonstrated a portal venous system connecting the median eminence in the hypothalamus with the anterior pituitary gland. Green and Harris[2] subsequently postulated the hypothalamic control of anterior pituitary function, probably by a neurohumeral mechanism. Later experimentation[3,4] using electrical stimulation or destruction of the hypothalamus or its pathways, demonstrated the hypothalamic control of pituitary follicle-stimulating hormone (FSH) and luteinising hormone (LH). This concept has been confirmed by the extraction from pig[5] and sheep[6] hypothalami of a highly purified peptide able to release both FSH and LH. It has since been identified as a decapeptide[7] which has recently been synthesised.[8] The availability of synthetic FSH/LH-releasing factor (FSH/LH-RF) during the past two years has led to a flurry of physiological studies on the control of gonadotrophin secretion. It appears that a single peptide controls both FSH and LH release[9] under normal circumstances, a larger amount of LH being discharged at a given dose of the releasing factor.[10] The presence of oestrogen appears to favour an effect on LH,[11] whereas in the prepubertal child there is greater tendency for FSH to respond.[10,12] Gonadotrophin release may be provoked before puberty,[10,12,13] even in infancy.[12] In rats, responsiveness of both FSH and LH to FSH/LH-RF increases until puberty, after which some decline occurs,[14] but a full study on age and gonadotrophin release in man has not yet appeared. There is a slightly greater gonadotrophin response to the releasing factor in the luteal phase of the menstrual cycle and a marked increase just before ovulation.[15] FSH/LH-RF does not appear to release any other pituitary hormone except occasionally growth hormone in acromegalics.[16] Clinically, it is being extensively used as a test of pituitary gonadotrophin reserve. In particular, it has been useful in distinguishing between delayed puberty (in which normal responses are obtained) and organic disease of the hypothalamus and pituitary in which responses are either flat or grossly attenuated.[10] In spite of the direct provocative effect on the anterior pituitary gland, patients with hypogonadism due to hypothalamic disease usually (but not always) fail to show normal response to FSH/LH-RF,[10] probably because the resting pituitary needs prior activation by endogenous releasing factor before responding to the exogenous administration of the peptide. In

this respect it is unlike hypothalamic hypothyroidism in which good TSH responses to thyrotrophin-releasing factor have been demonstrated.[17]

There is much interest in the therapeutic potential of FSH/LH-RF. It has been shown to induce ovulation in patients with secondary amenorrhoea previously unresponsive to clomiphene, in whom normal LH responses to FSH/LH-RF had been obtained.[9,18] Subsequent pregnancy has ensued without superovulation, suggesting that the more physiological levels of LH induced by this technique are less hazardous than those obtained by clomiphene or other hormonal regimens. Of greater import are the attempts to synthesise biologically inactive analogues of FSH/LH-RF which compete with the naturally occurring peptide for binding to the anterior pituitary, and so effectively act as contraceptive agents.[9] As the administration of the peptide appears to be singularly free of side-effects,[10] this approach to the problem of contraception is being assiduously explored in many centres.

B. L. PIMSTONE

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What's New in Osteoporosis?

Generalised osteoporosis is defined as a disorder of bone characterised by a progressive loss of bone mass until the skeleton is inadequate for mechanical support. The chemical composition of the remaining bone is virtually normal. The aetiology and the basic defects causing this common disease in elderly men and postmenopausal women remain speculative, but popular theories that have evolved have been the hormonal one, and disturbances of calcium metabolism. The hormonal theory was favoured by Albright because of the fact that an induced menopause was associated with the early development of osteoporosis, the presence of mild osteoporosis in hypogonadal states, and the beneficial effects of sex hormone therapy, especially oestrogens, on pain and calcium balance. Nordin, on the other hand, felt that a deficiency of calcium provoked osteoporosis. This deficiency could be caused by a combination of factors such as a low calcium intake, poor absorption and a high urinary loss. Another cause aggravating or precipitating such a disease state may well be vitamin D deficiency, with osteomalacia and not osteoporosis producing bone rarefaction, especially in the elderly. Subclinical hyperparathyroidism, perhaps resulting from an imbalance between the two calcium-regulating hormones, viz. parathyroid hormone and thyrocalcitonin, with the former being the predominant hormone, has also been postulated as a mechanism. Each of these theories can be made to seem plausible but they are not really mutually exclusive; some truth may well be in all of them.

There are a number of other unanswered questions; what is the exact role of aging? Why are only a certain number of people afflicted with the disease osteoporosis, despite the generally agreed fact that bone density decreases with age? Do these people have a reduced bone mass initially? Why are the elderly people of certain races practically exempt from the disease, e.g. Blacks? Why is it so difficult to replace bone mass and restore bone density despite large loads of calcium, and any other therapy one cares to mention, even when positive balance is achieved? What is the mechanism of bone pain? Why is the skull so rarely involved in generalised osteoporosis? Despite these

unsolved mysteries, some minor advances have been made in the therapy of this debilitating disease.

The beneficial effects of the hormone thyrocalcitonin, when used as therapy for conditions characterised by high rate of bone turnover, such as Paget's disease, and hypercalcaemia of diverse origins, have been demonstrated. Thyrocalcitonin inhibits bone resorption and thus has a tendency to produce hypocalcaemia and hypophosphataemia. It was appealing to explore the possibility of using synthetic thyrocalcitonin as therapy for osteoporosis where bone resorption exceeds bone formation. The optimism was dampened by a lack of response both in calcium balance and relief of bone pain to the administration of porcine and salmon thyrocalcitonin. The use of human thyrocalcitonin together with calcium and phosphate supplementation may offer advantages over the previous therapy and prove of benefit in the disease. One of the major disabilities endured by osteoporotic patients is severe back pain. Calcium infusions of 15 mg/kg body mass given intravenously in 1 litre of 5% dextrose water every 4 hours for 12 consecutive days, has been used successfully by Pak *et al.*[1] in the treatment of this symptom. Results at Groote Schuur Hospital have also been most encouraging, not only in the postmenopausal and idiopathic osteoporotic patient, but also in osteoporosis from iatrogenically induced hypercortisolism. The rationale for this therapy is that the hypercalcaemia produced will switch off non-autonomous subclinical hyperparathyroidism which may be producing the osteoporosis. One of the drawbacks of the therapy is the need for repeated courses.

The predominant effect of fluoride therapy on bone is osteoblastic stimulation. The mechanism of this effect is unknown, but it may be that fluorohydroxyapatite facilitates the passage of electric impulses, which stimulates osteoblasts. This reaction suggested that fluoride may be useful in the treatment of osteoporosis. However, the newly-formed bone was found to be poorly calcified, and osteomalacia and secondary hyperparathyroidism frequently coexisted. This therapy fell out of vogue until revived by Jowsey *et al.*,[2] who proposed the addition of vitamin D and calcium together with a smaller dose of fluoride to try to improve osteoporotic bone. The results to date with this therapy appear promising.

Lastly, what is the place of oestrogens in these new therapeutic schedules? They have a role in the treatment of postmenopausal osteoporosis in preventing bone demineralisation. It has also recently been shown that oestrogens tend to increase bone mineral content in postmenopausal females, provided they are given within 3 years after the onset of the menopause.[3] Perhaps they may be used with greater effect in combination with fluoride or calcitonin, or with added calcium and supplemented vitamin D. Clearly their therapeutic role has still to be defined, whereby they can be employed to their optimal advantage.

S. EPSTEIN

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