Little is known about the part that aluminium might play in pathological processes, but there is evidence that it need not be as inert as Wrong (1970) has argued. Gelfant (1963) used aluminium salts, especially chloride, as inhibitors of mitosis, while several workers have used aluminium salts in vitro to induce neurofibrillary spheroids and tangles in central and peripheral neurones (Klatzo *et al.*, 1965; Seil *et al.*, 1969). It is interesting to note that several patients with a high aluminium content in bone have also severe neuropathy, and studies of the deposition of aluminium in nervous tissue are under way.

Aluminium salts may also interfere with the orderly deposition of bone (Bachra and Van Harskamp, 1970) in that aluminium at concentrations of 1 μm or less can, by forming insoluble phosphates, initiate the precipitation of calcium apatite. Other clinical evidence (Nassim and Connolly, 1970) suggests that in the treatment of widespread soft-tissue calcification with aluminium hydroxide there is not only inhibition of further calcification but, over a period of two years, radiological evidence of a decrease in calcification with no evidence of the development of osteomalacia, though this can occur on such therapy.

Whether aluminium can influence the calcification processes in uraemic bone other than by phosphate depletion is unknown, but its deposition in uraemic patients could just be explained as the simple incorporation of an ion in excess as an "innocent bystander." But, in view of possible toxic effects, it is interesting to note that the aluminium concentrations found in one centre familiar with renal bone disease are among some of the highest reported, suggesting that there might be some causal effect.

There was no correlation between aluminium content and the amount of aluminium hydroxide taken, but on the whole the longer the patient had been uraemic and on dialysis the higher the concentration of aluminium. The rapid lowering of serum phosphate when aluminium hydroxide is given may partly be explained by the deposition of aluminium phosphate in tissue, including bone, rather than just the loss of phosphate in the gut as suggested by recent work at Charing Cross Hospital (Bailey *et al.*, 1971).

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MEDICAL MEMORANDA

Thyrotoxicosis Developing During Cyclophosphamide Therapy

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We report here the case of a woman who developed typical Graves's disease (thyrotoxicosis with goitre and ophthalmopathy) during a continuous five-month course of oral cyclophosphamide given for ovarian adenocarcinoma not radically removed by surgery. The evolution of thyrotoxicosis, a presumed autoimmune disorder, during systemic immunosuppressive therapy is of interest; an alternative possibility is that the tumour tissue was producing a humoral thyroid stimulant.

Case History

A 46-year-old woman was referred to the thyroid clinic at the Royal Infirmary, Glasgow, in August 1968 with a two-month history of 4 kg weight loss despite a good appetite. She disliked heat and sweated continuously. In addition she had developed exertional dysponea and palpitations and had become excessively nervous. There was no family history of thyroid disease.

She looked distinctly thyrotoxic, with bilateral lid retraction, exophthalmos, and periorbital puffiness. Her skin was warm and moist and she was hyperkinetic and had digital tremor. The thyroid gland was diffusely enlarged (40 g), with a systolic bruit. She had no pretibial myxoedema.

There was also pronounced capital alopecia due to oral cyclophosphamide therapy, which she had been taking continuously since February 1968 (6 months), when she had undergone a laparotomy for lower abdominal pain and palpable ovarian swellings. This operation had disclosed large bilateral ovarian neoplasms; the one on the right had ruptured, resulting in the deposition of malignant tissue in the pouch of Douglas, the anterior abdominal wall, and the posterior uterine wall. Subtotal hysterectomy, bilateral salpingo-oophorectomy, and removal of as much of the neoplastic tissue as was technically possible was undertaken. Histological examination of the surgical specimen showed that both ovaries were replaced by poorly differentiated adenocarcinoma with extensive necrotic and haemorrhagic areas. The metastases consisted of similar material. There was no evidence of struma ovarii or of teratomatous tissue.

The operation was not curative (since not all of the neoplastic tissue could be removed), and for this reason 600 mg of cyclophosphamide was instilled into the peritoneal cavity. In the immediate postoperative period she received 100 mg of cyclophosphamide intravenously; this was changed to 200 mg of cyclophosphamide by mouth by the second postoperative day. The dose of oral cyclophosphamide was reduced during her three weeks in hospital, and at the time of discharge she was taking 50 mg a day, which she took continuously till seen by us because of thyrotoxicosis.

Investigations carried out at the thyroid clinic in August confirmed the clinical diagnosis of thyrotoxicosis; the serum protein-bound iodine concentration was 10·4 μg/100 ml (normal 4-8 μg/100 ml). The uptake of a tracer dose of ^{131}I 24 hours after administration was 48% (normal 20-45%), and the 48-hour serum protein-bound ^{131}I was 3·83% of the dose per litre (normal less than

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0·3% of the dose per litre). Antibodies against thyroid microsomes were present in the serum in high concentration, but tests for serum anibody to thyroglobulin were negative. The haemoglobin was 12·2 g/100 ml and the erythrocyte sedimentation rate 9 mm in the first hour. The white cell count, repeated at follow-up clinic visits, was in the low normal range consistent with conrolled cyclophosphamide therapy.

On 23 August 15 mCi of ^{131}I was given as definitive therapy for the thyrotoxicosis. Bioassay for long-acting thyroid stimulator (LATS) (Kriss *et al.*, 1964) was performed on neat sera taken two weeks after radioiodine therapy. No LATS or thyroid-stimulator hormone (TSH) (McKenzie, 1958) activity was detected (lower limits of TSH assay 100 μU/ml). Three weeks after the radioiodine therapy carbimazole 30 mg daily was introduced to accelerate symptomatic control while awaiting the effect of the radioiodine therapy. Oral cyclophosphamide 50 mg daily was continued. Within eight weeks the patient's health improved considerably and she was euthyroid by January 1969, the carbimazole having been discontinued by that time. Her weight increased by 6 kg over this period but no alteration was noted in the size of the goitre and her exophthalmos did not regress.

Shortly after the improvement of her thyrotoxicosis she developed vaginal bleeding from an ulcer in the vaginal vault. Biopsy of this area disclosed anaplastic malignant cells. She was referred to palliative radiotherapy but her overall condition deteriorated rapidly and she died on 1 April. In her terminal illness she had developed jaundice, and at necropsy she had large hepatic metastases, which by their position had caused biliary obstruction.

Comment

Graves's disease is thought to be an autoimmune disorder (Hetzel, 1968). It has been suggested that LATS on immunoglobulin (IgG) produced by lymphoid tissues (McKenzie and Gordon, 1965) stimulates the thyroid (Adams, 1965). If LATS is an active immunoglobulin and the primary cause of Graves's disease the latter should not develop during immunosuppressive therapy. Glucocorticosteroids have been shown to cause the disappearance of LATS from the blood (Snyder *et al.*, 1964) and prednisone has produced a temporary remission of thyrotoxicosis in a small group of patients (Werner and Platman, 1965); prednisone has also been used with considerable success in the treatment of the ophthalmic complications of thyrotoxicosis (Werner, 1966). A fall in LATS can be induced by azathioprine (Hetzel, 1968) but the ophthalmopathy is not improved by this drug (Burrow *et al.*, 1970) and is only marginally improved by methotrexate (Werner, 1967).

The present patient developed thyrotoxicosis while on immunosuppressive therapy at a time when her ovarian carcinoma was in clinical remission, though tumour tissue was obviously still present in view of her rapid relapse and early death. Bioassay of LATS two weeks after radioiodine therapy, which often causes a rise in LATS (Adams, 1965; Lipman *et al.*, 1967), was negative; in our assay about half of the neat sera from thyrotoxic patients show LATS activity. We suggest, however, that LATS might not have appeared in this patient's circulation and that the thyrotoxicosis could have arisen despite immunosuppressive therapy.

Non-pituitary tumours, usually choriocarcinomas or seminomas, may secrete TSH (Odell *et al.*, 1963) or TSH-like material. These tumours usually cause biochemical rather than clinical thyrotoxicosis, and exophthalmos is very rare, though it has been described in a euthyroid patient with a seminoma (Mann, 1967). Cancer chemotherapy usually improves the biochemical abnormalities. It is recognized that the McKenzie assay (1958) is not a sensitive test for serum TSH; using this technique we were not able to detect any TSH activity in the serum, and radioimmunoassay for TSH was not carried out. The patient died in another hospital and at necropsy no tumour was retained for TSH assay. It is thus possible that the tumour was secreting a TSH-like material which did not cross-react in the McKenzie assay. We think this aetiology is unlikely, because the patient had florid clinical thyrotoxicosis, exophthalmos, and serum antithyroid antibodies. These features are much more consistent with the presumed autoimmune type of hyperthyroidism (Graves's disease).

A recent case report (Chopra and Solomon, 1970) showed some of the difficulties in accepting autoimmunity as the cause of thyrotoxicosis. The patient, who had been under surveillance for several years, had pretibial myxoedema and ophthalmopathy with high levels of circulating LATS, and over the original period of observation she was not thyrotoxic. While under supervision she did become thyrotoxic, but the circulating level of LATS paradoxically fell at this time. The authors thought that the thyroid abnormality was intrinsic, and Goldberg *et al.* (1953) suggested that there is an intrinsic self-regulatory mechanism in the thyroid which is independent of pituitary TSH secretion. Presumably this internal thyroid regulation can be malset and lead to autonomous hypersecretion, but obviously further work is necessary before this concept can be definitely accepted. Meanwhile the present patient's Graves's disease, arising as it did during chemical immunosuppressive therapy, suggests that autoimmunity and LATS production might not alone account for the disorder.

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