their normal range. Finally, eight months after the initial episode a standard glucose tolerance test gave normal values.

It thus appears that the hyperglycemia and glycosuria observed in this patient were related to the DPH toxicity and were mediated by a mechanism other than that operating in the stressed "pre-diabetic" subject. Several possibilities seem to exist. Release of ACTH has been reported to be inhibited[3] and plasma 17-hydroxycorticoid levels low or normal[1] in patients receiving DPH, so it seems unlikely that the pituitary-adrenal axis mediated the observed effect. Epinephrine infusion has been shown to inhibit release of pancreatic insulin,[4,5] thereby potentiating the hepatic glycogenolytic hyperglycemia also induced. Not to my knowledge, however, has the production of sustained hyperglycemia via this mechanism been documented in acutely stressed patients.

Finally, a direct effect of DPH on the pancreatic release of insulin can be postulated. Woodbury[12] suggested that DPH exerts its anticonvulsant action by diminishing the intracellular sodium content of the brain, thereby lowering excitability. He also noted the stimulating effect of DPH on cellular sodium-extruding processes in cardiac and skeletal muscle. This observation is of interest in view of the well-known hyperglycemic effect of the thiazide diuretics.[9] The mechanism of their hyperglycemic action remains unclear, but intracellular potassium depletion appears to be a possible explanation, at least in part.[7] It is thus tempting to speculate that the effect of DPH in the present case was similarly mediated via an induced alteration in the electrolyte concentration of the pancreatic islet cells, thereby inhibiting insulin secretion.

Summary

The occurrence and remission of hyperglycemia and glycosuria in conjunction with diphenylhydantoin (DPH) toxicity in a non-diabetic patient is described. No similar cases were found in the literature. An inhibitory effect of DPH on insulin secretion by the pancreatic islet cells is one of several possible explanatory mechanisms.

GENERIC AND TRADE NAME OF DRUG

Diphenylhydantoin—*Dilantin.*®

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Gynecomastia Associated with Vincristine Therapy

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Vincristine (Oncovin®), a chemotherapeutic agent derived from the periwinkle plant (vinca rosea Linn), has been demonstrated to induce remissions in various neoplastic diseases including myeloproliferative and lymphoproliferative syn-

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dromes.[1] Adverse reactions to the drug are common, with neurologic deficits predominant in frequency and severity.[3] While using vincristine we observed a previously unreported side effect, gynecomastia, which occurred in two of twenty adult male patients receiving this drug for four weeks or longer.

Reports of Cases

CASE 1.—A 30-year-old white man, previously normal except for unilateral testicular atrophy associated with varicocele, was found to have stage III Hodgkin's disease in September 1963. During the ensuing year he received repeated courses of radiation therapy and three courses of nitrogen mustard therapy. Upon exacerbation of the disease, he was treated with weekly intravenous injections of vincristine from December 1964 to March 1965. On 8 February 1965, after four doses of vincristine, 0.04 mg per kg of body weight per week, gynecomastia was noted in the form of a 2×4 cm tender, hypertrophied mass beneath the areolar area of the right breast. The dosage was halved at that time, but two weeks later the opposite breast was similarly involved. One month later, despite continuing therapy, the masses had decreased in size. Following discontinuation of the drug at the end of March, the masses were smaller and nontender. Subsequently, the masses disappeared, although the patient's clinical course indicated continued activity of Hodgkin's disease.

CASE 2.—A 57-year-old Malaysian man was found to have reticulum cell sarcoma upon biopsy of a left cervical mass in July 1964. The cervical areas bilaterally and the mediastinum were treated initially with radiation. The abdomen was also irradiated after resection of an obstructing cecal lesion in February 1965. By early April 1965, a right cervical mass was noted. The patient was dysarthric and had a right cranial nerve palsy. On 23 April, vincristine therapy was begun in a dose of 0.025 mg per kg of body weight per week. By 24 May, paresthesias had developed in both hands and there was a tender 4×4 cm mass beneath the areola of the left breast. Significantly, the dysarthria improved and the neck mass decreased in size. By 22 July both breasts contained firm, tender, hypertrophied subareolar tissue and on biopsy of the mass in the left breast the typical histologic features of gynecomastia were seen. Urine 17-keto and 17-hydroxy corticoid determinations as well as gonadotropin determinations were within normal limits. By 30 August, despite continued treatment with vincristine, the breast masses had decreased in size and subsequently they disappeared. The patient remained well while receiving vincristine therapy, without evidence of tumor recurrence or gynecomastia.

Discussion

Gynecomastia is defined as an enlargement of the male breast with round cell infiltration, proliferation of connective tissue and mammary ducts and absence of encapsulation.[6] It is manifested clinically by a tender mass underlying the nipple and areola and may be associated with secretion of colostrum. This condition is to be distinguished from mammoplasia, occurring in adolescent and senescent males, in which the tenderness and chronic inflammatory infiltration is lacking.[2]

A list of medications associated with gynecomastia previously reported is tabulated in Table 1.[4,5] We were unable to find reports of gynecomastia associated with either Hodgkin's disease or reticulum cell sarcoma, although actual tumor invasion has been reported with these and other malignant diseases. Repeated careful evaluation of the two patients in this report failed to reveal any other apparent cause of gynecomastia. Development of the condition several weeks after the beginning of vincristine therapy strongly suggests a casual relationship with drug administration. This annoying, but minor, side effect appears to be transient in nature and may disappear during continuation of therapy.

Summary

Bilateral gynecomastia developed in two men while they were receiving vincristine therapy for malignant disease. In one case, biopsy showed the lesion to be histologically typical of gynecomastia. The condition was transient, the lesions subsiding despite continuation of therapy. These two cases

TABLE 1.—*Drugs and Hormones Associated with Development of Gynecomastia*

Estrogens	Gonadotropins
Androgens	Anterior pituitary extract
Desoxycorticosterone	Amphetamines
Digitalis	Reserpine
Isoniazid	Radioiodine
Griseofulvin	Oleandomycin
Spironolactone	Tetracycline
Progesterone	

suggest that gynecomastia may appear as a side effect of vincristine therapy, that it is transient in nature and that breast enlargement during such therapy need not be considered evidence of neoplastic involvement.

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