period in the first test was taken as 100% the mean (± S.E. of the mean) change found in the second test was 13·25% (±6·0%) for the plateau acid output, 7·85% (±5·81%) for the peak acid output, and 13·88% (±9·14%) for the total acid output.

Discussion

Our data indicate that the administration of insulin by a continuous infusion technique does produce a steady-state acid secretion in response to a steady level of hypoglycaemia.

Although additional dose-response data will be required our initial trial indicates that a dose of 0·04 U of insulin/kg/hr produces the highest plateau of acid secretion associated with relatively few hypoglycaemic symptoms. It also appears important not to prolong the fasting period over 12 hours.

It is as yet too early to reach any definitive conclusions about the ultimate value of the continuous insulin infusion test, but it already appears safe and is associated with few side effects. It is hoped that by producing a steady state as opposed to a peak secretory response its interpretation will be facilitated.

The applicability of the criteria currently used for the conventional Hollander test (Hollander, 1946) and the definition of new criteria are at present being evaluated.

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MEDICAL MEMORANDA

Parathyroid Hormone Production and Malignancy

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We report relatively large amounts of parathyroid hormone found in extracts of a retroperitoneal sarcoma and in a hepatic metastasis from a carcinoma of the breast; neither tumour has previously been implicated in this syndrome (Omenn *et al.*, 1969). This hormone production by cancers of non-endocrine origin is now well recognized (Lipsett *et al.*, 1964).

Case Reports

Case 1.—A woman aged 52 presented with a lump in the outer quadrant of the right breast in February 1965. A radical mastectomy was performed and metastases in lymph nodes were found. After radiotherapy she was well until September, when pain developed in the right epigastrium and an enlarged liver was detected. Shortly after this she began to vomit and was admitted to hospital, where serum calcium was found to be 21·6 mg/100 ml, serum phosphorus 3·3 mg/100 ml, and serum alkaline phosphatase 26 K.A. units/100 ml. After treatment with intravenous fluids and corticosteroids the serum calcium fell slowly to a minimum of 12·0 mg then rose again to 14·5 mg/100 ml. No bony metastases were found radiologically. Her condition deteriorated and she died on 1 November. Before her death serum phosphorus reached 5·5 mg/100 ml, serum alkaline phosphatase 52 K.A. units/100 ml, and blood urea 110 mg/100 ml. At necropsy, 28 hours after her death, the liver weighed 4,070 g and was heavily infiltrated with tumour. No metastases were found in any other organ, and none were found in bone or bone marrow. The two parathyroid glands found were normal. Histological examination of the liver showed many oval irregular epithelial cells forming irregular tubules and acini consistent with metastatic carcinoma from a primary breast tumour.

Case 2.—A man aged 61 was admitted to another hospital in December 1966 with dementia, slurred speech, and vomiting. Hypercalcaemia (13·5 mg/100 ml) was discovered and parathyroid exploration undertaken. Two normal parathyroid glands were found. In January 1967 a firm mass was found in the right loin and operation showed what appeared to be an inoperable carcinoma of the kidney. Hypercalcaemia persisted despite high doses of corticosteroids. He was admitted to the Royal Melbourne Hospital on 7 February, where he was found to be emaciated and confused. A large irregular mass was present in the right loin. Serum calcium was 21·4 mg/100 ml on admission and serum phosphorus ranged from 1·7 to 2·4 mg/100 ml. Treatment with intravenous sodium phosphate temporarily restored serum calcium to normal but it quickly rose again. Immediately before death serum calcium was 18·0 mg, serum phosphorus 4·3 mg, and blood urea 232 mg/100 ml, and serum alkaline phosphatase was 19 K.A. units. No lesions were detected radiologically in his bones. Necropsy two hours after death disclosed a huge haemorrhagic and necrotic retroperitoneal tumour invading the right kidney, adrenal, liver, and surrounding muscle. The vertebrae were not involved. Small nodular metastases were present in the lungs. Microscopically the tumour consisted of bands of long cells, often spindle-shaped and poorly defined.

Tissue Assay and Results

Normal or malignant tissue was obtained at necropsy or at operation and frozen. The frozen material was lyophilized, powdered, defatted with acetone, and dried under vacuum. Extraction was performed with phenol (Aurbach, 1959) or urea-hydrochloric acid-cysteine (Rasmussen *et al.*, 1964) to the stage of solvent precipitation, for which ether was used. The precipitate was washed with acetone, extracted with acetic acid, and immunoassayed. Antisera to parathyroid hormone were

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prepared by injecting about 1,000 units of partially purified bovine parathyroid hormone emulsified with Freund's adjuvant into guinea-pigs at intervals of two to four weeks. Highly purified bovine parathyroid hormone (kindly supplied by Drs. J. T. Potts, jun., and G. D. Aurbach) was used for iodination and as standard. ^{125}I and ^{131}I were supplied by the Radiochemical Centre, Amersham. The radioimmunoassay was carried out as described by Berson *et al.* (1963) except that charcoal-dextran was used to separate antibody-bound labelled parathyroid hormone from free tracer (Melick and Martin, 1968, 1971). Extracts were assayed on several occasions in at least three dilutions. Recovery experiments performed with the extracts gave satisfactory yields, indicating that they were not interfering with the assay. Results are expressed as μg equivalents of bovine parathyroid hormone per gram of tissue (wet weight).

Extracts from normal uterus, ovary, stomach, liver, lung, and brain, and from carcinomatous lymph nodes (metastasis from stomach, lung, and adrenal) showed minimal (0·01 μg/g) or no material reacting like parathyroid hormone. All of the patients providing these tissues were normocalcaemic. The extracts of the tumours of both the present patients contained large amounts of immunologically active material. The curves obtained with the extracts were not identical with the standard curve given by bovine parathyroid hormone but the tumour in Case 2 was estimated to contain between 0·3 and 0·55 μg of bovine parathyroid hormone/g and that in Case 1 from 1·8 to 2·0 μg/g. An extract of apparently normal liver from Case 1 gave a value one-twentieth that of the tumour (0·01 μg/g) but neoplastic infiltration of this tissue could not be excluded. For comparison a human parathyroid adenoma was found to contain about 60 μg of bovine parathyroid hormone/g.

Comment

Omenn *et al.* (1969) reviewed 73 cases of hyperparathyroidism associated with malignant tumours of non-parathyroid origin. The two tumours reported here, carcinoma of the breast and retroperitoneal sarcoma, were not included in their list. Katz *et al.* (1970), in describing primary hyperparathyroidism in patients with breast cancer, commented on the frequency of hypercalcaemia in that condition and on the absence of any report of the occurrence of parathyroid hormone-like material in a cancer arising from the breast.

It is perhaps relevant to mention here a recent case discussed at the Massachusetts General Hospital (1971) where, despite the presence of a squamous carcinoma, hypercalcaemia, and hypophosphataemia, parathyroid hormone could not be detected in plasma or in extracts of the tumour. No metastases were found in bone at necropsy, but histologically there was much resorption of bone. A non-parathyroid bone-resorbing agent cannot be excluded.

The immunological differences between human and bovine parathyroid hormone make quantitative interpretation of these results difficult (O'Riordan *et al.*, 1969). Despite this, however, the results found were similar to the values reported by Sherwood *et al.* (1967) of 0·75 to 8·93 μg of parathyroid hormone /g of tissue, and that by Knill-Jones *et al.* (1970) of 1·3 μg/g of tissue. These amounts fall well short of those found in parathyroid tissue but probably represent less than that originally present owing to the time lapse between death and freezing of the tissue. In addition these tumours were many times the size of the usual parathyroid tumour.

These findings suggest that parathyroid hormone production by cancers may be more common than suspected on clinical grounds. The addition of two more cancers to the list of those associated with the syndrome indicates the need for careful consideration of the diagnosis of ectopic parathyroid hormone production in hypercalcaemic states, particularly those in which malignancy is suspected. Improved assay methods should help in determining the frequency of the syndrome.

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Addendum.—Since this report was prepared Mavligit *et. al.* (1971) have reported the production of parathyroid hormone by a breast cancer.

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