time, however, for her bone disease. Blood gas studies excluded a venous-arterial shunt.

In October 1964, a barium swallow done during investigation of an anæmia revealed a large (symptomless) tumour of the œsophagus. Calcium-47 tracer studies were carried out before and after excision of the tumour, to provide objective measurements of the severity of the bone disease by which post-operative progress could be judged.

At operation, a 70 gram polypoid tumour was removed from the lower end of the œsophagus. Histologically this proved to be a benign fibrous polyp. By the third post-operative day all joints were free of pain and full function was restored. Peripheral circulation, previously excessive, diminished to normal and by the seventh day the soft-tissue swelling at wrists and ankles had reduced circumferentially by 3·2 cm.

The uptake of ^{47}Ca locally by hypertrophic bone was measured and compared with that by relatively unaffected bone. Expressed as a ratio $\frac{\text{abnormal bone}}{\text{normal bone}}$, the pre-operative figure of 1·31 ± 0·01 fell to 1·08 ± 0·01 ten weeks post-operatively. This suggests a lessening of her skeletal disease as a result of removing the tumour. Studies of calcium kinetics (North *et al.* 1962) showed an increased exchangeable calcium pool (Ca_E = 27 plasma units) with very high bone accretion rate (Ca_B = 6·5 plasma units), none of which showed significant change ten weeks post-operatively. It is perhaps too early for changes in locally affected areas to be reflected in measurements of overall skeletal kinetics.

Clinically, the early post-operative improvement has continued, and after ten weeks the clubbing has regressed almost to normal. The peripheral blood flow, measured in the forearm, has fallen from 11 ml/100 ml/min pre-operatively, to 4·4 ml/100 ml/min (N = < 4·5 ml/100 ml/min). Radiologically, no bone change is evident yet. The ulcerative colitis remains an independent problem.

Discussion

Hypertrophic osteoarthropathy has been described in association with various lesions of the œsophagus – achalasia of the cardia (Preble 1898) and carcinoma (Cayla *et al.* 1962, Peyman 1959).

The immediate relief of bone pain, and regression of clubbing, has been frequently recorded in cases of pulmonary neoplasm following thoracotomy (Holling 1961), or vagotomy (Flavell 1956), even though the tumour be left undisturbed. Merely sectioning the intercostal nerves may produce similarly dramatic results (Holman 1963).

It is not possible to state, therefore, whether the improvement in our patient resulted from loss of the tumour, or from the process of its removal. It seems likely, however, that the œsophageal tumour was responsible for her bone disease. The mechanism by which this might occur is unknown, but it seems necessary to invoke an endocrine influence to explain the generalized nature of her skeletal disease. The tumour is to be assayed for biological activity.

Acknowledgments: Our thanks are due to Dr Nelson Coghill for the opportunity to study this patient, and to Dr J Ginsberg and Dr A Guz for their assistance in special investigations.

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Hyperinsulinism due to Metastasizing Insulinoma: Treatment with Diazoxide

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The treatment of intractable hypoglycæmia, whether due to malignant insulinoma or to other causes, has hitherto been unsatisfactory. Though many substances have been tried, none has been effective. The brilliant application by Drash & Wolff (1964) of diazoxide – a non-diuretic benzothiadiazine, withdrawn as a potential anti-hypertensive therapeutic agent because of its hyperglycæmic side-effects – to the management of such cases, offers new promise.

The patient presented is a 51-year-old car salesman. After a three-months illness he was diagnosed, in October 1964, as suffering from metastatic insulinoma. At laparotomy the primary tumour in the tail of the pancreas was removed,

but at least two hepatic metastases were left behind. The propensity to develop fasting hypoglycæmia was uninfluenced, and three-hourly feeds were necessary to prevent the occurrence of episodes with loss of consciousness, blood glucose levels after a three to four hour fast being in the region of 20–30 mg/100 ml. Prednisone in large doses was tried without effect. Therapy with diazoxide – 600 mg/day, reduced to 400 mg/day after one week – was instituted in November 1964 with immediate benefit. Normoglycæmia was restored; overnight fasting was well tolerated and blood glucose levels after a twelve to fourteen hour fast were consistently between 70 and 90 mg/100 ml. Apart from nausea for two days whilst on the larger dose (600 mg/day), there have been no untoward side-effects from this drug.

The patient returned to work in January 1965 and has been subjectively in perfect health since treatment began. His diet, appetite and weight are now (June 1965) the same as before the onset of the illness.

The results of investigations designed to determine the mode of action of diazoxide will be published in greater detail elsewhere. Volume of distribution of glucose increased 50%. Fasting plasma insulin, which was initially high, began gradually to fall after four days on diazoxide, eventually reaching normal levels at which it has remained.

Peripheral glucose utilization, markedly impaired at first, improved with time, and was possibly the major factor contributing to the rise in the fasting blood glucose concentration, though the fall in plasma insulin, which occurred later, undoubtedly served to maintain the therapeutic response.

Fasting plasma non-esterified fatty acids (NEFA) did not rise significantly except during a short period of excessive hyperglycæmia which occurred with the larger dose of diazoxide.

These results differ from those reported by Ernesti *et al.* (1965) in a similar case, possibly due to their use, in addition to diazoxide, of other hyperglycæmic agents, including diuretic benzothiadiazines which enhance the blood glucose raising properties of diazoxide (Wolff & Parmley 1963), but not necessarily in the same way.

Preliminary studies in a further patient with hypoglycæmia due to glycogen storage disease, and encouraging reports of the usefulness of diazoxide in the treatment of other varieties of hypoglycæmia which are unamenable to specific curative therapy (Drash & Wolff 1964) suggest that further trials of the drug, either alone or in combination with diuretic benzothiadiazines, are amply justified.

Acknowledgments: We should like to thank Dr W T Simpson of Allen & Hanburys Ltd for supplying diazoxide.

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Addison's Disease with Vitiligo, Addisonian Anæmia, Primary Hypothyroidism and Diabetes Mellitus

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Mrs J N, aged 58

History: Presented March 1962 with a loss of 30 lb in weight in eight months, anorexia, vomiting and weakness.

Family history: Mother died of addisonian anæmia. Husband's sister diabetic.

On examination (March 1962): Generalized pigmentation of skin and vitiligo on upper limbs and back, sunburn having not faded after the previous summer. Tender in loins. Blood pressure 140/95. Right lobe of thyroid just palpable. Scanty pubic hair, no axillary hair.

Investigations: Urinalysis normal. Serum sodium 147, potassium 6·1, chlorides 105 mEq/l. Blood urea 18 mg/100 ml. Water excretion 20% of load in four hours, 80% after 50 mg cortisone acetate. Urinary 17-ketosteroids 2·5, 17-hydroxycorticosteroids 6·5 mg/24 h; no increase after corticotrophin zinc or ACTH gel. X-rays of chest and suprarenal areas, barium meal and follow through, normal. Tuberculin reaction positive. Radioiodine tests: urinary excretion 56% in forty-eight hours, 'T' 3·4. Serum PB ^{127}I 2·2–2·5 μg/100 ml, unchanged after 10 units thyroid stimulating hormone on two successive days. Serum cholesterol 215 mg/100 ml. Hb 12·7 g/100 ml, PCV 35%, MCHC 36%, MCV 117 cu.μ. WBC 4,700 (neutros. 71%, lymphos. 24%, monos. 5%). Histamine-fast achlorhydria. Sternal marrow megaloblastic. Serum vitamin B_{12} 20 μμg/100 ml. Reticulocytes 12% after six days' treatment with vitamin B_{12}. ESR 25–30 mm in 1 h (Westergren).