two groups of patients directly since detailed diagnostic information is lacking in their reports. A similar overlap in protein bound iodine and free thyroxine index is also observed between patients with hypothyroidism and normal subjects (Evered *et al.*, 1973).

The estimation of serum T-3 concentration appears to discriminate well between normal subjects and those with hyperthyroidism in all series and the range of T-3 concentrations appears to be similar in all the groups studied by all workers with mean values between 4.2 and 5.2 ng/ml. Subjects with minor degrees of hyperthyroidism, however, appear to have been excluded in the preliminary studies of serum T-3 concentrations reported. The discriminant value of this estimation in the diagnosis of hyperthyroidism remains to be definitely established. Raised serum T-3 concentrations have also been observed in other clinical situations which will be described elsewhere.

There is the generally expected correlation between serum T-4 and T-3 concentrations, and the relation between the concentrations of the two thyroid hormones in the serum is very similar to that reported by Larsen (1972a). The only general deviation from this correlation is seen in the subjects with T-3 thyrotoxicosis, and also in some other clinical states.

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Vitamin B₁₂ Malabsorption after Cobalt Teletherapy for Carcinoma of the Bladder

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Summary

After cobalt teletherapy for carcinoma of the bladder, eight out of 14 consecutively admitted patients were shown to have malabsorption of vitamin B₁₂, though none had developed a megaloblastic anaemia. Despite lack of symptoms this group of patients is at risk after radiotherapy.

Introduction

Cobalt teletherapy is an accepted method of treating infiltrating carcinoma of the bladder. The small bowel lies in the field of irradiation and since it is highly radiosensitive intestinal complications after treatment sometimes occur. Those of stenosis, obstruction, perforation, or fistulation of the small bowel are well known, and from animal and clinical observations it has been realized for some time that malabsorption can also occur (Dodds and Webster, 1924; Martin and Rogers, 1924; Buchwald, 1931; Salvesan and Kobro, 1939; Moss, 1957; Scudamore and Green, 1959; Sauer, 1959; Wood *et al.*, 1963; Duncan and Leonard, 1965). Irradiated bowel has frequently been observed at laparotomy to be rigid and thickened and histologically there is mucosal atrophy and submucosal

fibrosis (Halls, 1965). The terminal ileum lies in the pelvis, is the most frequently involved segment of gut (Dodge, 1969), and is wholly responsible for B₁₂ absorption (Booth and Mollin, 1959). Surprisingly few cases of malabsorption of this vitamin after pelvic irradiation have been recorded. A number of patients with carcinoma of the bladder at St. Thomas's Hospital who were referred for cobalt teletherapy were studied to assess the degree to which malabsorption of vitamin B₁₂ occurred after this form of treatment.

Patients and Methods

The patients were interviewed when they attended hospital for follow-up cystoscopy between December 1969 and May 1970. They had all had cobalt teletherapy for stage II or stage III carcinoma of the bladder, each receiving a tumour and tissue maximum dose of 3,600 r and a minimum dose of 3,100 r. Most were given six treatments in 18 days using a four-field technique—anterior and posterior with two laterals—to cover the whole true pelvis. A history was taken and they were examined clinically for signs of metastatic disease or abdominal abnormality.

The haemoglobin and serum B₁₂ concentrations and the plasma urea were measured.

The absorption of vitamin B₁₂ was estimated by the Schilling test modified by the addition of intrinsic factor. A dose of 0.5 µg ⁵⁷Co B₁₂ was given by mouth with 1 U.S.N.F. unit of hog intrinsic factor (supplied by Radiochemical Centre, Amersham). One and a half hours later a flushing dose of 1,000 µg of vitamin B₁₂ was given intramuscularly. The 24-hour urine specimen was

obtained during the patient's stay in hospital, the bladder being completely emptied at the end of the collection period. An excretion of more than 7% of the orally administered dose was regarded as normal.

Patients who had undergone ileal resection, who had advanced malignant disease, or who had raised plasma urea were excluded from the study.

Results

Altogether, 14 patients were available for assessment and the results are shown in the table.

Details of Patients Studied after Radiotherapy

No. of Patients	Vitamin B ₁₂ Absorption	Mean Age (Years)	Time After Radiotherapy (Months)	
			Range	Mean
6 (43%)	Normal	63.8	1-44	22.6
8 (57%)	Reduced	59.4	2-112	24.3

Six patients (five male, one female) had normal vitamin B₁₂ absorption and eight patients (seven male, one female) had impaired B₁₂ absorption (see chart). The mean age and the mean time after radiotherapy of these groups were similar.

Excretion of ⁵⁷Co-labelled vitamin B₁₂ in 14 patients with carcinoma of the bladder after radiotherapy.

Nearly all patients admitted having loose frequent bowel actions for a short time immediately after radiotherapy but this usually settled spontaneously. Two patients had occasional loose stools and both these were in the group with abnormal Schilling test findings. None of the patients had any other significant symptoms or signs and none had had previous abdominal surgery. All the patients had normal haemoglobin, serum B₁₂, and plasma urea concentrations.

Discussion

Intestinal malabsorption may present with diarrhoea, anaemia, and weight loss, and the few reported cases of B₁₂ malabsorption after radiotherapy had severe symptoms, were ill, and had extensive damage to the small bowel (Duncan and Leonard, 1965; Tankel *et al.*, 1965; Ratzkowski and Hochman, 1968). Altogether, 57% of the present series had B₁₂ malabsorption after pelvic irradiation and these patients were largely asymptomatic.

There were no cases of advanced malignant disease which is sometimes associated with malabsorption (Dymock, 1966). Barium studies were not performed as most of the patients gave a history of normal bowel function and it is probable that none of them had any degree of stricture formation severe enough to form a blind loop: this cause of malabsorption, however, cannot be excluded in the two patients who had mild symptoms.

Adhesions from previous lower abdominal surgery anchoring the small bowel in the pelvis have been held responsible for the occurrence of serious intestinal damage after pelvic irradiation (Ashbaugh and Owens, 1963; Halls, 1965; Tankel *et al.*, 1965; Edwards, 1968). In the present survey, however, none of the patients had had any abdominal operations and it is clear that the terminal ileum can be damaged sufficiently to produce B₁₂ malabsorption even in the absence of adhesions.

It appears that malabsorption can occur at any time after radiotherapy. Duncan and Leonard (1965) reported four cases of B₁₂ malabsorption two, five, seven and 24 months after treatment. Three of their patients presented with megaloblastic anaemia and one of these with subacute combined degeneration of the cord. Tankel *et al.* (1965) reported two patients with evidence of deficient B₁₂ absorption three and nine months after irradiation. Ratzkowski and Hochman (1968) reported that B₁₂ absorption was reduced in one third of their 40 patients, most of whom were severely ill and had had variable dosages and fields of irradiation. However, as three out of the six patients who had the Schilling test repeated with intrinsic factor were found to have pernicious anaemia, it is difficult to draw any conclusions from their work. In the present study B₁₂ malabsorption measured by the Schilling test with intrinsic factor was found to be present from two to 112 months after radiotherapy.

The incidence of damage to the small bowel after pelvic radiotherapy is difficult to assess. Mason *et al.* (1970) reported an incidence of 0.6-17% for all cases of chronic radiation enteritis but these figures include the more frequently involved rectum and sigmoid colon. Experimental methods of protecting the bowel from radiation have been attempted by some workers (Steckel *et al.*, 1968; Bosniak *et al.*, 1969) but these are not effective in practice. Probably a certain dose of radiation to the small bowel is inevitable during the treatment of bladder carcinoma. With accurate measurement of the fields and dosage and with careful positioning of the patient, this can be reduced to a minimum.

In normal subjects the body stores of vitamin B₁₂ are large and may take several years to become depleted. Indeed it may take up to 10 years to develop a megaloblastic anaemia after a total gastrectomy. None of the patients in this series was anaemic at the time of investigation but this would not be expected as the period of follow-up was relatively short. Though they all had normal serum B₁₂ concentrations several were in the low normal range and it is possible that some of these patients will become overtly vitamin B₁₂ deficient. It is important that clinicians should be aware that anaemia developing in asymptomatic patients who have had pelvic teletherapy may be due to malabsorption and not necessarily to recurrent or metastatic disease.

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Recurrent Hyperkalaemia due to Selective Aldosterone Deficiency: Correction by Angiotensin Infusion

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Summary

A patient with recurrent weakness and blurring of consciousness associated with hyperkalaemia due to aldosterone deficiency is reported. The plasma concentrations of renin, angiotensin II, and aldosterone were low and did not increase during sodium deprivation. Blood angiotensin I was also low while renin-substrate concentration was normal. Infusion of angiotensin produced a distinct rise in plasma aldosterone. The patient was treated successfully with fludrocortisol.

The results support the concept that the renin-angiotensin system is an important regulator of aldosterone secretion and that in the syndrome of acquired selective hypoaldosteronism the primary abnormality may be a deficiency of renin. It is suggested that a selective lack of aldosterone should be considered in all cases of otherwise unexplained hyperkalaemia.

Introduction

The association of acquired aldosterone deficiency with normal cortisol levels was first reported by Hudson *et al.* (1957). The syndrome seems to be rare since only 21 further cases have been recorded (Skanse and Hokfelt, 1958; Hill *et al.*, 1959; Lambrew *et al.*, 1961; Rick *et al.*, 1962; Posner and Jacobs, 1964; Wilson and Goetz, 1964; Gerstein *et al.*, 1968; Vagnucci, 1969; McGiff *et al.*, 1970; Vagnucci, 1970; Ferrara *et al.*, 1970; Perez *et al.*, 1972; Schambelan *et al.*, 1972; Mellinger *et al.*, 1972; Weidman *et al.*, 1972; Brown *et al.*, 1972a).

In some instances the deficiency of aldosterone was attributed, at least in part, to a biosynthetic block (Vagnucci, 1969; Jacobs and Posner, 1964; Perez *et al.*, 1971); in most of the others the pathogenesis remained completely obscure.

The objectives of the present paper are two-fold; firstly, to report another case of this rare but easily treatable condition, and, secondly, to provide evidence supporting the concept first

mentioned by Jacobs and Posner (1964) and subsequently by others (Wilson and Goetz, 1964; Gerstein *et al.*, 1968; Vagnucci, 1969; McGiff *et al.*, 1970; Ferrara *et al.*, 1970; Perez *et al.*, 1972; Schambelan *et al.*, 1972; Weidman *et al.*, 1972) that the aldosterone deficiency is secondary to suppression of the renin-angiotensin system.

Some of our observations in this patient have been reported in brief elsewhere (Brown *et al.*, 1972a; 1972b). We present here a fuller account including the necropsy and histological findings.

Methods

Most of the laboratory methods used were those listed in a recent publication (Brown *et al.*, 1972c). The additional techniques used were: blood angiotensin I concentration, Waite (1972, 1973) (normal range 11-88, mean 51 pg/ml); plasma renin-substrate, Tree (1973) (normal female range 0.45-1.28, mean 0.85 μ mol); plasma "cortisol" by a competitive protein binding technique of Murphy (1967) (normal range at 09.00 hours: 6-18, mean 11.8 μ g/100 ml); urine free cortisol, Beardwell *et al.* (1968) (normal range up to 110, mean 42 μ g/day); and kidney renin extraction, Tree (1972).

The special clinical techniques used were: angiotensin infusion, Chinn and Dusterdieck (1971), using synthetic as¹ val⁵ angiotensin II, Hypertensin-Ciba; tests of autonomic function, Johnson *et al.* (1971); tests of ability to decrease or increase urine pH with NH₄Cl (Wrong and Davies, 1959) and acetazolamide (Counihan *et al.*, 1954) respectively.

Case History

The patient, a woman of 81, had remained in good health until early 1971 when she was referred to hospital elsewhere complaining of unusual tiredness, generalized weakness, loss of weight, constipation, and pain with stiffness particularly affecting the wrists and the hand joints. Apart from some swelling around the interphalangeal joints, there were no abnormal features on examination (blood pressure 164/76 mm Hg). Investigation showed a normal blood count (Hb 13.2 g/100 ml, W.B.C. 7,300/mm³, E.S.R. 12 mm in one hour) and a midstream urine without protein, reducing substance, or growth on culture. A chest x-ray film, intravenous urography, barium meal and barium enema examination showed nothing abnormal. The serum potassium concentration was initially normal (4.0 mEq/l.) but during the next few weeks the level increased to 7.0 mEq/l. accompanied by a small fall in serum Na to 138 mEq/l. and an appreciable rise in blood urea (80-122 mg/100 ml). At that stage oral treatment with a cation exchange resin—sodium polystyrene sulphonate (Resonium-A) 45 g/day—and sodium bicarbonate (20 g/day) resulted in a prompt return of the serum electrolytes and blood urea to more normal levels.

The patient was then discharged from hospital and remained

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