more often by spasm of the umbilical cord vessels due to manipulation and cooling (Rhodes, 1956).

Various authors have commented on the adverse effect of a long detection–delivery interval on the perinatal mortality, and it has been shown that after one hour there is a rapid rise in mortality (Fenton and D'Esopo, 1951 ; Ball *et al.*, 1961 ; Winch and Claman, 1961 ; Nelson and Burns, 1963 ; Widholm and Nieminen, 1963 ; Sinnathuray, 1964). In a small series of 15 cases Campbell (1962) quotes an average detection–delivery interval of 8 minutes 20 seconds for vaginal delivery and 28 minutes for caesarean section. To reduce the foetal loss in prolapsed cord it is necessary to have adequate facilities, so that caesarean section or any other treatment can be initiated immediately the diagnosis is made. Routine vaginal examination as soon as the membranes rupture, irrespective of the presenting part and irrespective of its level, will favour early diagnosis and reduce the all-important time lag between the occurrence of cord prolapse and initiation of the appropriate treatment.

The late prognosis for the survivors of cord prolapse was assessed by Cushner (1961), and 95% of those located were normal. It seems that, provided the infant is delivered alive and survives the neonatal period, no harm is done by the possible period of anoxia before delivery associated with cord prolapse.

Summary

Fifty cases of cord prolapse occurring in the last two years are analysed and compared with the results obtained 12 years ago in the same unit.

Caesarean section is superior to all other forms of treatment ; in the series surveyed it resulted in a very low perinatal mortality.

It is unlikely that cord prolapse will ever be eliminated as a cause of perinatal mortality.

I thank Mr. J. J. Foley, Mr. F. A. Murray, and Mr. C. W. Gale for permission to publish these figures. I acknowledge the part played by the various members of the medical and nursing staffs in the care of the patients.

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Preliminary Communications

Effect of Mithramycin on Calcium and Hydroxyproline Metabolism in Patients with Malignant Disease

Brit. med. J., 1967, **1**, 474–477

Mithramycin is an antibiotic with cytotoxic activity derived from an actinomycete culture belonging to the genus *Streptomyces*. The activity of the drug, like that of actinomycin D, is thought to be the inhibition of D.N.A.-directed R.N.A. synthesis (Yarbro, Kennedy, and Barnum, 1966).

The activity probably depends upon stoichiometric occlusion within the D.N.A. helix, preventing R.N.A. replication and indirectly the synthesis of protein involved in enzyme production (Goldberg, 1965). Preliminary findings in a clinical trial of mithramycin led us to anticipate disturbances in calcium metabolism which had occurred when this drug was used to treat patients with testicular malignant disease (Brown and Kennedy, 1965).

Methods

A variety of patients with malignant disease, with and without bone metastases seen radiologically, were treated with mithramycin as part of a clinical trial (Baum and Mackay, 1966). Several patients were already in an advanced state of malignant disease, but none had a blood urea higher than 60 mg./100 ml. Patients were given a full ward diet, which did not include excessive quantities of gelatin ; their daily diet was supplemented by oral calcium galactogluconate (Sandoz) containing 760 mg. of elemental calcium. Mithramycin was given at a dosage of 25 μg./kg. in 0.45% saline by continuous infusion for eight days. In three patients (Cases 1, 4, and 6) a shorter course was given because of the onset of severe vomiting.

Twenty-four-hour collections of urine were made under toluene with added hydrochloric acid. Blood was taken before noon in each patient daily for a series of haematological and biochemical estimations. Eleven patients were treated in this way and five more had in addition 100,000 or 200,000 units of calciferol for 24 hours before and throughout treatment with mithramycin. Urine and serum were analysed for calcium by flame photometry (MacIntyre, 1961) for phosphorus (Fiske and Subbarow, 1925), while the urine was also analysed for creatinine (Nordin and Smith, 1965) and total hydroxyproline by the method of Prockop and Udenfriend (1960). Serum was also analysed for alkaline phosphatase and other enzymes, but, as no attempt was made to study bone as distinct from tumour alkaline phosphatase, the results are not included.

Owing to a degree of nausea and anorexia, fluid and food intake were reduced in a number of patients, leading to a fall in urinary output, but calcium supplements were maintained in all patients.

Results

The Table shows the age, sex, type of tumour, presence of bone metastases, dose of mithramycin, initial serum calcium concentration, and 24-hour output of urinary calcium hydroxyproline. Fig. 1 shows plots of progressive changes in plasma

calcium concentrations, Fig. 2 urinary calcium/creatinine ratios, and Fig. 3 hydroxyproline/creatinine ratios. The first 11 patients are regarded as a single population and standard deviations are included.

Patients Treated with Mithramycin, Showing the Dose and Investigations Prior to Treatment

Case No.	Age and Sex	Primary Tumour	Radiological Bone Metastases	Total Dose Mithramycin (mg.)	Initial Values: Serum Ca (mg./100 ml.)	Initial Values: Urinary Ca (mg./24 hr.)	Initial Values: Urinary Hydroxyproline (mg./24 hr.)
1	52 F	Adenocarcinoma of breast	Yes	6·4	10·7	95	27
2	75 F	Adenocarcinoma of rectum	No	10·9	11·1	138	33
3	50 M	Squamous-cell bronchus	Yes	11·2	8·8	492	144
4	78 F	Adenocarcinoma of breast	Yes	9·2	8·8	369	89
5	53 M	Anaplastic carcinoma of bronchus	No	14·0	8·7	313	45
6	50 M	Squamous-cell bronchus	Yes	5·2	12·3	372	56
7	64 F	Adenocarcinoma of breast	No	13·0	10·8	162	35
8	52 F	" "	No	10·0	10·5	230	49
9	83 F	" "	Yes	9·5	10·4	69	15
10	63 M	Adenocarcinoma of rectum	No	12·5	13·7	75	
11	42 F	" "	No	13·3	9·4	262	64
12*	61 F	Adenocarcinoma of ovary	No	10·0	8·4	43	72
13*	63 F	Adenocarcinoma of rectum	No	14·0	13·1	181	55
14*	48 M	Fibrosarcoma of pelvis	No	10·0	11·6	208	65
15*	54 M	Hypernephroma	No	12·6	10·6	88	51
16*	62 M	? Bronchus	No	11·2	11·0	350	50

* Received vitamin D.

Cases 12–16 had 100,000 or 200,000 i.u. of vitamin D and their mean daily results are shown in each of the figures as an interrupted line. No significant changes were noted in the plasma phosphate concentrations. The urinary calcium/creatinine excretion ratio as shown in Fig. 2 is expressed as mg./g. creatinine used to correct for declining urinary volumes, unobserved errors in collection, and the wide range of age and surface area of the patients (Nordin, 1959).

Discussion

The findings of an overall decrease in serum calcium reflected by an acute reduction in urinary calcium and a moderate reduction in urinary hydroxyproline excretion during treatment with mithramycin are the result of several possible mechanisms.

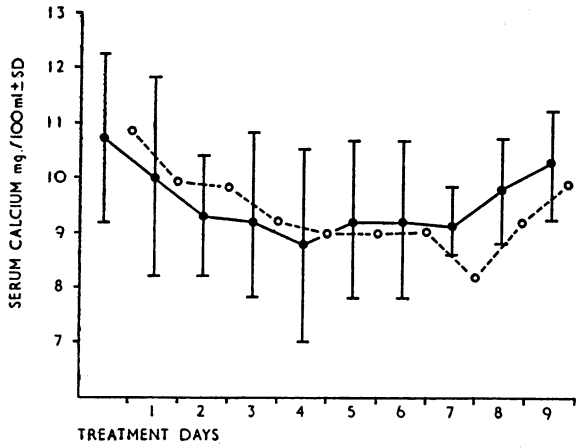

FIG 1.—Serum calcium concentrations one day before and eight days during treatment. - - - Patients also treated with vitamin D.

The first to consider is the effect of tumour regression, which was observed in some patients but not all; this may have led to rapid bone healing and a drain on the plasma and extracellular fluid pool of calcium, but for this to be maintained a failure of parathyroid hormone action must be invoked as well. This type of change is illustrated in a patient who developed spontaneous hypocalcaemia with osteoblastic metastases where partial hypoparathyroidism was also believed to be present owing to raised serum phosphate concentrations (Ehrlich, Goldstein, and Heinemann, 1963). However, raised serum phosphate concentrations in excess of 4 mg./100 ml. were not seen at any time during treatment in this series. Rapid healing of bone is usually accompanied by increased hydroxyproline turnover and excretion, which was not seen in any of these patients treated with mithramycin.

Gordan, Cantino, Erhardt, Hansen, and Lubich (1966) have reported finding an osteolytic sterol in breast cancer which increased the output of calcium from labelled parathyroidectomized rats' bones. It is possible that mithramycin might affect the output of this sterol, reducing osteolysis and the supply of calcium to the plasma and indirectly to the urine, but once again parathyroid hormone homoeostasis would also be

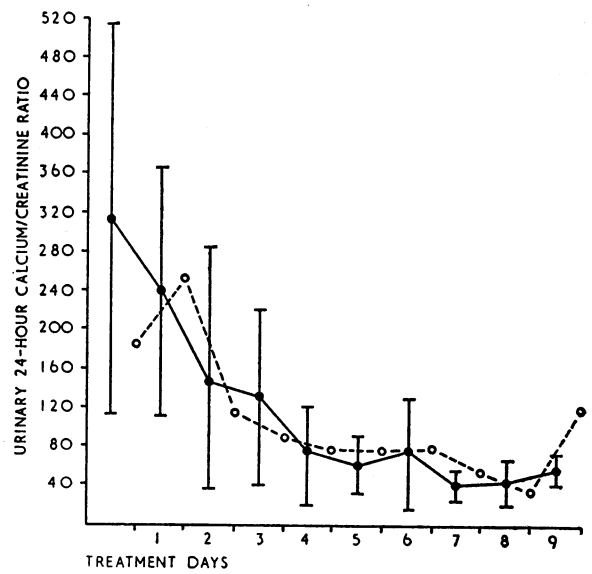

FIG. 2.—Urinary calcium/creatinine ratios (mg./g. creatinine) excreted each day. - - - - Patients also treated with vitamin D.

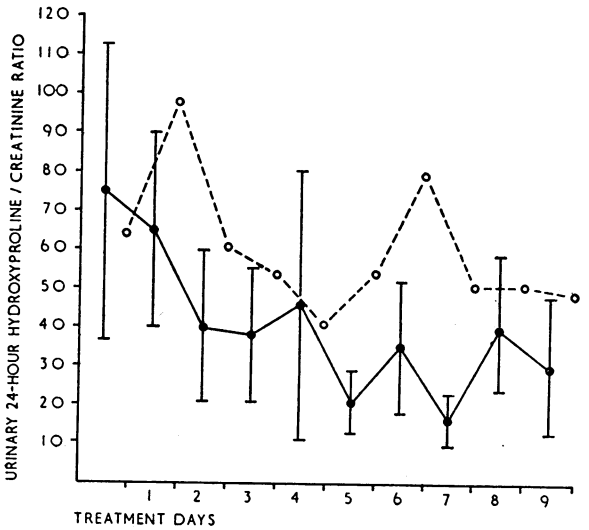

FIG. 3.—Total urinary hydroxyproline/creatinine ratios mg./g. creatinine excreted each day. - - - - Patients also treated with vitamin D.

faulty, as the hypercalcaemic patients (Cases 2, 6, and 10) did not have carcinoma of the breast, nor show greater falls of serum calcium than the patients who were normocalcaemic. None of the patients had a urinary output of calcium, hypercalcaemia, or hypophosphataemia, suggesting that their tumours were producing parathyroid hormone-like peptides described in some patients with malignant disease (Bower and Gordan, 1965). Thus a reduction in hormone-like peptides or osteolytic sterol need not be regarded as one of the actions of mithramycin in this series.

The second mechanism to consider is the action of this actinomycin-D-like substance on the hormonal control of calcium metabolism directly. Actinomycin D inhibits the action of parathyroid hormone in raising the serum calcium in parathyroidectomized rats (Rasmussen, Arnaud, and Hawker, 1964), blocks the hypercalcaemic effect of large doses of vitamin D (Eisenstein and Passavoy, 1964), and inhibits the action of vitamin D on the intestinal absorption of calcium (Zull, Czarnowska-Misztal, and De Luca, 1965). This latter inhibition has been investigated more thoroughly by Harrison and Harrison (1966), who showed that actinomycin D blocked the transport of calcium across the mucosal surface of vitamin-D-deficient as well as vitamin-D-treated rats, an action on the transport system itself rather than on the stimulatory effects of vitamin D on the system—no influence was noted on the transport across the mucosal preparation of L-tyrosine.

Further studies on the action of actinomycin D have shown that the maximum hypocalcaemic effect was apparent only 12 and 18 hours after administration and that the parathyroid glands from these hypocalcaemic rats were still capable of sustaining the serum calcium when transplanted into parathyroidectomized rats (Tashjian, 1965). The hypocalcaemic effect of thyrocalcitonin was not blocked under similar conditions. This finding suggests that there is no direct blocking effect on synthesis of the parathyroid hormone in the parathyroid gland, placing the main effect of actinomycin more peripherally. This observation is pertinent because it has been suggested that, as in many patients with malignant disease, hypertrophy of the parathyroid glands has been noted at necropsy, this finding may be related to the hypercalcaemia accompanying metastases (Kohout, 1966).

The slight but frequently observed recovery of the serum calcium concentrations towards the end of the treatment period might suggest that the unopposed and unblocked action of thyrocalcitonin, induced by the relative hypercalcaemia in several patients, cuts off as the hypercalcaemia is reduced by the action of mithramycin. The reduced urinary volumes, anorexia, and recovery of the serum calcium might also be due to the blocking of sterol synthesis by mithramycin—an action already ascribed to actinomycin D (Farese, 1966), but no consistent electrolyte abnormalities have been observed in our patients.

The excretion of hydroxyproline is raised at the outset in the majority of patients, in keeping with the excretion pattern in malignant disease (Platt, Doolittle, and Hartshorn, 1964; Gruson, Ryckewaert, Hioco, Lanham, and De Sèze, 1966; Bonadonna, Merlino, Myers, and Sonenberg, 1966). Urinary hydroxyproline excretion correlates with isotope measures of bone resorption, the majority of urinary hydroxyproline being derived from bone collagen (Heaney, 1964; Klein, Lafferty, Pearson, and Curtiss, 1964; Smith and Nordin, 1964), though some may originate from a small pool of recently synthesized collagen (Hosley and Taft, 1965). The calcium hydroxyproline ratio falls under treatment with mithramycin because the fall in urinary calcium is more precipate than that of hydroxyproline. This could be explained on the basis that the fall in serum calcium is not only the result of lowered bone resorption but also due to decreased gut absorption of calcium, the latter having no effect on hydroxyproline excretion.

Hydroxyproline excretion in some patients fell to very low concentrations (10 mg./24 hours), and in these cases there may have been inhibition of collagen synthesis as well as breakdown (Owen, 1966). There is the unknown contribution from the collagen metabolism within the tumour tissue, but the only correlation between the tumour and observed hydroxyproline excretion seems to be hypercalcaemia (Bonadonna *et al.*, 1966) or bony involvement (Gruson *et al.*, 1966), rather than the type or size of the tumour. The hypocalcaemic effects of mithramycin cannot be reversed by giving large quantities of vitamin D (100,000 to 200,000 units daily) by mouth, which would have been expected to raise the serum calcium in normal subjects over a similar period of time. The serum calcium fell from hypercalcaemic values in two patients given mithramycin and vitamin D and remained above 7 mg./100 ml. in the remainder. The urinary calcium showed similar changes mirroring the serum calcium, while the calcium/hydroxyproline ratio decreased, suggesting that the blocking effect on the gut had not been reversed by vitamin D.

Studies of calcium kinetics in malignant disease (Bentzel, Carbone, and Rosenberg, 1964) suggest that there may already be an excessive loss of calcium into the gut, accounting for the frequent finding of a negative calcium balance. Few studies suggest vitamin-D resisitance, but osteomalacia may be seen near secondary deposits in bone (Follis, 1954). In our findings it does not appear that the development of hypocalcaemia in malignant disease treated with mithramycin can be overcome by large doses of vitamin D. Conversely, mithramycin alone can reduce the hypercalcaemia of malignant disease, and can be included in the series of agents already in use, such as phosphate (Goldsmith and Ingbar, 1966) and steroids (Bentzel *et al.*, 1964).

SUMMARY

Mithramycin, an actinomycin-D-like antitumour agent, is shown to have a consistent hypocalcaemic effect leading to a fall in urinary calcium excretion despite a sustained calcium intake. Urinary hydroxyproline output, raised in a proportion of patients with malignant disease, also falls under treatment with mithramycin. These findings suggest that mithramycin blocks the peripheral action of parathyroid hormone on gut and bone, either by direct action or by making the patients vitamin-D-resistant. The administration of high doses of vitamin D did not reverse these effects.

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Medical Memoranda

Childhood Nephrosis Followed by Acute Glomerulonephritis in Adulthood

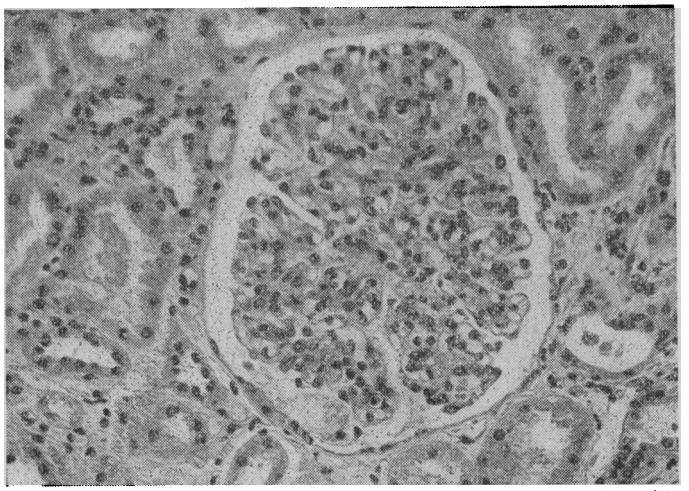
Brit. med. J., 1967, 1, 477

The causes of lipoid nephrosis and acute glomerulonephritis are still poorly understood, and it remains uncertain whether any relation exists between these entities. We have recently observed a patient in whom the sequential occurrence of the two diseases took place.

Case Report

A 46-year-old man was admitted to hospital because of swelling of the ankles. He had been well until the onset of oedema of the face and legs three weeks previously. There was no history of pharyngitis, fever, shortness of breath, headache, oliguria, or haematuria. He had been in hospital 36 years previously after six months of anasarca. Records of that admission indicated marked oedema of the abdominal wall and lower extremities, ascites, and heavy proteinuria without haematuria; recovery was complete after six weeks in hospital. He passed Army physical examinations 24 and 19 years ago, and negative urinalyses were obtained by a private physician eight and seven years ago.

Physical examination on admission showed him to be well developed, well nourished, and in no apparent distress. Mild periorbital oedema was evident. His temperature was 98.6° F. (37° C.), pulse 52, respirations 20, and blood pressure 120/70 mm. Hg.



Photomicrograph of renal biopsy specimen showing a glomerulus with increased cellularity and prominent endothelial cells.

Cervical veins were not distended and the lungs were clear. The heart was not enlarged. Two-plus soft pitting peripheral oedema was present. The urine gave a two-plus test for protein; the sediment contained numerous red blood cells, 2–4 white cells per high-power field, and a few red cell casts. Antistreptolysin, antihyaluronidase, and antistreptodornase titres were normal. Streptococci could not be isolated from the nasopharyngeal passages. Blood urea nitrogen was 18 mg./100 ml. The 24-hour urine protein output was 249 mg.

The haematocrit was 34%; the white-cell count, differential, and E.S.R. were normal. *X*-ray examination of the chest showed the heart to be at the upper limits of normal in size. Intravenous urography was normal. An electrocardiogram showed sinus bradycardia. Renal biopsy performed on the fifth hospital day showed acute proliferative glomerulonephritis but gave no evidence of chronic renal disease (see Fig.).

Penicillin was given for 10 days. Diuresis of 14 lb. (6.4 kg.) occurred, with a rise in haematocrit from 34 to 42% and disappearance of oedema. At the time of discharge (two weeks after admission) the urine gave a negative reaction for protein and had a specific gravity of 1026; the sediment contained 2–4 red cells per high-power field. The blood urea nitrogen was 22 mg./100 ml., and the creatinine 1.5 mg./100 ml.

Discussion

The clinical and histological features of this case are typical of acute glomerulonephritis (Jennings and Earle, 1961), though no proof of recent streptococcal infection could be obtained. The childhood episode appears characteristic of lipoid nephrosis. Though acute glomerulonephritis causing the nephrotic syndrome cannot be excluded with certainty, complete recovery after six months of anasarca and the absence of haematuria militate against this diagnosis (Lawrence *et al.*, 1963). The sequential occurrence of these two diseases in the same patient is apparently a rare phenomenon; we have found no report of a similar case. The fact that one kidney can show evidence of both conditions is of interest because it suggests that the causes of the two disease states are distinct or that the organism's pattern of response to a given stimulus may alter with age.

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