matory exudates to inhibit inflammatory reactions forms part of the body's normal mechanism for limiting and terminating acute inflammatory reactions (DiPasquale and Girerd, 1961; DiPasquale *et al.*, 1963; Robinson and Robson, 1964, 1966, 1967). Hence it was thought desirable to investigate whether a similar situation existed in man.

In this investigation an inflammatory exudate of human origin was shown to inhibit markedly an experimental inflammatory reaction (see Table I). This anti-inflammatory effect is not attributable simply to the injection of a foreign protein, since human serum and an ascites fluid were virtually devoid of anti-inflammatory activity. Another possible explanation is that the anti-inflammatory activity of partial gastrectomy exudate is due to the action of corticosteroids either present in the exudate or released in the recipient rats. Although at the moment we have no direct evidence to disprove this hypothesis, we do know that the exudate collected from adrenalectomized rats, and shown fluorimetrically to contain no corticosteroids (Billingham, 1968), markedly inhibits experimental inflammation in both intact and adrenalectomized recipient rats. It has not been possible to assess fluorimetrically the corticosteroid levels of the human exudates, since the haemolysis that is usually seen with these renders accurate estimation impossible. Nevertheless, the exudates collected immediately postoperatively, at a time when a higher level of steroid would be expected, have less anti-inflammatory activity than exudates collected subsequently. It seems more likely that the active component of human exudate, rather than being a steroid, is similar to the anti-inflammatory substance in animal exudates—that is, a protein. As evidence of this the similarities discussed below between the anti-inflammatory properties of inflammatory exudates of human and animal origin add some weight to the possibility of the active components being related.

The time of appearance of anti-inflammatory activity, in both types of inflammatory exudate, is remarkably similar in respect of both the rise in activity during the first few days and the time at which maximal activity is reached. With regard to its chemical nature the anti-inflammatory component of both inflammatory exudates is non-dialysable—that is, it behaves as a macromolecule. Both human inflammatory exudate and that from the rat fractionate in a similar fashion when subjected to Sephadex G 150 gel filtration. Furthermore, the anti-inflammatory activity appears in a similar position on the elution diagram—that is, in pools 2 and 3 (see Fig. 2 and Table II). It is possible, therefore, that the anti-inflammatory activity of human inflammatory exudate, as has been suggested for the rat, forms part of the body mechanisms involved in limiting and terminating acute inflammatory reactions.

Looking to the future, it is hoped to purify the anti-inflammatory substance of human origin at least to the stage reached with the anti-inflammatory substance obtained from the rat. The purification of the rat material has reached the point where 3 mg. of purified material produces a similar anti-inflammatory effect—that is, inhibition of oedema—to that produced by 100 mg. of the whole inflammatory exudate (Billingham *et al.*, 1969). On a weight-for-weight basis the purified rat material, though still far from pure, is as active as hydrocortisone.

It is hoped that ultimately the anti-inflammatory substance of human inflammatory exudate, when purified, may be of use clinically in the treatment of chronic inflammatory diseases.

We would like to thank Mr. S. A. R. Cooke, senior surgical registrar, and the nursing staff of the surgical wards of Guy's Hospital for providing us with the inflammatory exudates. We also thank the Arthritis and Rheumatism Council, the Peel Medical Research Fund, and the Guy's Hospital Endowments Fund for financial support.

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Medical Memoranda

Hypercalciuria in Sarcoidosis Treated with Inorganic Phosphates

British Medical Journal, 1969, **2**, 96–98

Hypercalciuria and hypercalcaemia are of particular importance, since they may lead to calculus formation or nephrocalcinosis and renal failure, hypercalcaemia being one of the most definite indications for corticosteroid therapy (Scadding, 1967).

The use of inorganic phosphate in the case described below was prompted by persistent hypercalciuria, which was only poorly controlled by large doses of prednisone.

CASE HISTORY

A man aged 30 was admitted to hospital on 31 August 1965 complaining of cough, dyspnoea, and loss of 1 st. (6.4 kg.) in weight over the previous two months. Clinical examination showed nothing abnormal.

Investigations.—Chest x-ray examination showed widespread bilateral nodulation with hilar gland enlargement. Tuberculin skin test (100 T.U.) was negative. Liver biopsy showed follicles of the sarcoid type. Serum calcium was 9.5 mg./100 ml.; 24-hour urine calcium 810 and 1,000 mg.; alkaline phosphatase 13.5 K.A. units; total plasma proteins 7.5 g./100 ml. (albumin 4.1 g., globulin 3.4 g.). Electrophoresis showed slight increase in α_2 -globulin. The gas transfer factor of the lung for carbon monoxide (TlCO) at rest was 9.5 ml. CO/min./mm. Hg at 13.8 l./min. During exercise it was

15.9 ml. CO/min./mm. Hg at 32.5 l./min. The predicted T_{LCO} at rest was 22.1 ml. CO/min./mm. Hg. Hb was 91%, E.S.R. 44 mm. in one hour.

The patient remained well and was discharged on 10 September. He was readmitted, however, on 24 June 1966 after an episode of haematuria with pain in the right iliac fossa. Until then he had had no symptoms.

An abdominal x-ray film showed shadows of calcific density overlying the lower aspect of the left kidney and linear densities in the line of the right ureter. Serum calcium was 10.5 mg./100 ml., inorganic phosphate 4.4 mg./100 ml., alkaline phosphatase 9.6 K.A. units, 24-hour urine calcium 1,150 mg., and creatinine clearance 125 ml./min. Chest x-ray examination showed the development of fibrosis in the upper zones.

Treatment with prednisone (30 mg. daily) to reduce the urinary calcium excretion was started on 28 July with prompt effect, the urine calcium falling to 240 mg./24 hours (see Chart). On 1 August he passed two urinary calculi. The prednisone dosage was later reduced to 15 mg. daily, but the urinary calcium excretion gradually rose to 580 mg./24 hours. A further period of treatment, as an outpatient, with 30 mg. daily produced a small fall in urinary calcium, but because of the development of Cushingoid features it was discontinued after four months of therapy. This was followed by a rapid increase in urinary calcium excretion over the next 10 weeks to levels of 1,000 mg./24 hours, the serum level remaining normal.

He was again readmitted and put on a low calcium diet (423 mg. daily)—it had been noted that his normal diet contained considerable quantities of cheese and milk—but the 24-hour urine calcium remained between 710 and 810 mg. Abdominal x-ray and I.V.P. films showed multiple bilateral small calculi in the minor renal calices. The creatinine clearance was 91 ml./min. Chest x-ray examination revealed persistence of hilar gland enlargement and considerable mid-zone fibrosis. The T_{LCO} at rest and on exercise was unchanged.

In view of the continued hypercalciuria and renal calculus formation plus the progressive lung fibrosis prednisone (30 mg. daily) was started again. A small fall in urinary calcium was noted but was not maintained when the dose was reduced to a more reasonable level (10 mg. daily) for long-term therapy. On 21 November 1967 therapy with a mixture of inorganic phosphates (anhydrous Na_2HPO_4) containing 1 g. of phosphorus element per 60 ml. was begun in a dose of 30 ml. t.d.s., in addition to the prednisone (10 mg. daily). Within two weeks the urinary calcium excretion had decreased markedly, levels of between 160 and 260 mg./24 hours being maintained. The serum calcium levels remained within normal limits, and increasing the daily dietary calcium intake to 1 g./day caused no significant effect.

The patient continued on this treatment and diet without any side-effects and returned to work. The urinary calcium four months after starting phosphate therapy was 160 mg./24 hours and the serum level was 9.2 mg./100 ml.

Corticosteroid therapy was continued (prednisone 10 mg. daily) to try to prevent further lung fibrosis, and it is of note that although

the dose used was not effective in suppressing the high urine calcium output there was a significant improvement in gas transfer with a T_{LCO} at rest of 15.7 ml./min./mm. Hg at 8.8 l./min., and during exercise of 20.4 ml./min./mm. Hg at 20.8 l./min.

COMMENT

Hypercalciuria is a common complication of sarcoidosis, and occurs much more frequently than hypercalcaemia. Hirsch (1961) noted hypercalciuria in 50% of 24 cases, while hypercalcaemia occurred in only 15% of about 200 patients. Sharma *et al.* (1967) concluded that hypercalciuria was three times more common than hypercalcaemia, and that urine analysis is the more sensitive of the two techniques for detecting abnormal calcium metabolism.

There is considerable evidence to show that some patients with sarcoidosis have increased intestinal absorption of calcium. This is thought to be due to increased sensitivity to normal quantities of vitamin D (Anderson *et al.*, 1954; Henneman *et al.*, 1956; Bell *et al.*, 1964). It is apparent, however, that changes in the serum and urinary calcium levels are to some extent independently determined, and Jackson and Dancaister (1959) suggested that the hypercalciuria might be caused by a renal tubular defect with compensatory overabsorption of calcium.

The ability of corticosteroids to correct the abnormal calcium metabolism in sarcoidosis has proved diagnostically and therapeutically extremely useful. General measures which should be advised, but may be overlooked, are the reduction of the dietary intake of calcium and the avoidance of extra vitamin D, either ingested or as a result of exposure to sunlight. Because of side-effects or, as in this case, their relative ineffectiveness, long-term corticosteroid therapy may be contraindicated. Other forms of treatment therefore need to be considered.

Hunt and Yendt (1963) used chloroquine to treat a case of sarcoidosis with hypercalcaemia and hypercalciuria, and found it took three months before the urinary calcium excretion became normal.

Sodium phytate was recommended as "the treatment of choice of the hypercalciuria of sarcoid" by Henneman *et al.* (1956), though in one of his cases combined therapy with cortisone and sodium phytate failed to reduce the daily urinary calcium excretion below 400 mg.

The nephrotoxicity of sodium edetate prohibits its prolonged use in the hypercalciuria of sarcoidosis.

Administration of sodium salts of phosphate and sulphate mainly by infusion has been reported in the treatment of hypercalcaemia of diverse aetiologies (Bulger *et al.*, 1930; Chakmakjian and Bethune, 1966; Goldsmith and Ingbar, 1966). Sodium sulphate reduces the serum calcium by increasing urinary excretion, and would obviously be contraindicated in the presence of hypercalciuria. The mechanism of action of phosphate is not fully understood, but renal excretion of calcium is reduced. This might be due to bony or ectopic calcification. Dent (1962), using much larger oral doses of disodium hydrogen phosphate (15 g. daily) than in our case for the treatment of hypercalcaemia of hyperparathyroidism, reported the development of painful ectopic calcification, but this may have been due to the protracted hypercalcaemia alone. Goldsmith and Ingbar (1966), however, using intravenous and oral phosphate in the treatment of 20 cases of hypercalcaemia of diverse aetiologies, concluded that metastatic calcification was not a necessary complication of phosphate therapy.

In our case a prompt fall in calcium excretion in the urine greatly reduced the risk of further calculus formation. Ectopic calcification may not be a problem in the absence of prolonged hypercalcaemia.

The indications for treating uncomplicated hypercalciuria in patients with normocalcaemia are not established. About 8%

of the general population have levels of urinary calcium excretion higher than the normal range suggested by Hodgkinson and Pyrah (1958)—100–300 mg./24 hours for males, and 100–250 mg./24 hours for females (on a normal diet)—and the relation between high urinary excretions of calcium and the formation of calcium-containing stones is not definitely established. Whether the risks of stone formation are higher in normocalcaemic hypercalciuric patients with sarcoidosis is also unknown. However, Sharma *et al.* (1967) concluded that the natural history of the calcium derangement is dependent on the type of sarcoidosis. In the patients presenting with erythema nodosum or bilateral hilar lymphadenopathy the calcium metabolism always reverted to normal. In the group with pulmonary fibrosis the calcium abnormalities persisted. Hypercalciuria occurring in this latter group might therefore require treatment even in the absence of hypercalcaemia or urinary calculi in order to prevent stone formation.

I acknowledge with thanks the help given by Dr. K. M. Citron, under whose care the patient was admitted to the Brompton Hospital.

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Perforation of the Nasal Septum in Systemic Lupus Erythematosus

British Medical Journal, 1969, 2, 98

Perforation of the nasal septum may be caused by various infections including syphilis, tuberculosis, and leprosy. Other causes are industrial exposure to certain dusts, such as those containing chromium, phosphorus, iodine, and cement. It may also be the result of congenital anomalies, trauma, malignant disease, granulomatous states, and diseases of the blood. But we could find no reports of systemic lupus erythematosus (S.L.E.) as a cause. No reference to it appears in the studies by Dubois and Tuffanelli (1964), Larson (1961), and Shulman and Harvey (1960). We report a case here.

CASE REPORT

A 36-year-old housewife presented in 1957 with a raised temperature, dyspnoea, tiredness, malaise, and weakness. The family history and her previous history contained nothing relevant. Enlarged lymph nodes and pleural effusion on both sides later appeared. The erythrocyte sedimentation rate was 62–92 mm. in one hour. On electrophoresis the amount of gammaglobulins was always above 30%; the rheumatoid factor was negative. The patient had already been examined twice for the L.E. phenomenon, with negative results. But as the disease was believed to be systemic lupus erythematosus treatment with antimalarial drugs was started. In 1959 arthritis of the rheumatoid type appeared. There was myalgia, and tests for the rheumatoid factor were now positive. One further test for the L.E. phenomenon was negative. In 1960 the L.E. phenomenon was found to be positive for the first time, with hypergammaglobulinaemia 47.7% and a butterfly rash. Laboratory tests now showed the disease to be highly active. The thymol turbidity reaction was positive and there was thrombocytopenia (80,000/cu. mm.). There was a false-positive Wassermann reaction.

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From 1958 to 1964 the patient had received steroids three times, but never for longer than three months. Treatment with anti-malarial drugs was continuous, and salicylates were given when needed.

In 1965 hemiparesis, diplopia, and psychotic symptoms were noted, all probably caused by arteritis. Five tests for the L.E. phenomenon were still positive. The thymol turbidity reaction was sometimes positive and also the latex-fixation test, but with a low titre. The leucocyte counts were repeatedly lower than 5,000/cu. mm. Signs of right heart failure were evident from the end of 1966. In 1967 leg ulcers appeared on both sides. There was livedo reticularis, more breathlessness, clubbing of the fingers, and sometimes nose bleeding. When the leg ulcers appeared she also complained of pain in her nose.

She was examined by Dr. S. Sadecky, otolaryngologist, who reported: "The septum of the nose is lightly deviated to the right, and the mucous membrane is red and dry; in the centre part of the septum there is a defect of about 10 mm. surrounded by crusts, a perforating ulcer of the nasal septum." As the mucous membrane was fragile and infected, histological examination was not undertaken. This state remained unchanged up to September 1968.

Comment.—We believe that our record is the first to be described of perforation of the nasal septum in S.L.E. Even so we doubt whether it is a rare manifestation of S.L.E., but suspect that it has been overlooked.

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