mithramycin infusions which had been carried out the year previously. Apart from her bone pain the patient was in good health but with a strong family history of rheumatoid arthritis and thyroid disease. The patient had previously had a partial thyroidectomy for colloid goitre and a cholecystectomy.

A skeletal survey revealed Paget's disease confined to the left radius and tibia. The disease was active as judged by an elevated serum alkaline phosphatase and urinary hydroxyproline concentration as well as an increased uptake of radioactive strontium in the diseased bone. Because of the bone pain, treatment with synthetic salmon calcitonin (Calcynar) 50 MRCu (approx. 12·5 μg) twice daily subcutaneously, was instituted (Woodhouse, Reiner & others, 1971; Woodhouse, 1974). There was an immediate and sustained fall in urinary total hydroxyproline concentrations. Within a week the patient reported complete relief of bone pain and this, together with a biochemical remission of the disease, has been sustained on treatment for the last 116 weeks (Fig. 1).

In April, 1975, after 84 weeks on treatment, the patient noticed pains in the shoulders, elbows, wrists, knee and ankle joints. This was associated with weakness and lethargy, a reduced Hb of 11·7 g dl^{-1} an elevated ESR of 45 mm in the first hour and a positive rheumatoid factor at a dilution of 1/64. Straw coloured fluid was aspirated from an effusion in the right knee. No crystals were seen and the serum uric acid concentrations were normal at 0·28 mmol $litre^{-1}$. A diagnosis of rheumatoid arthritis was made and soluble aspirin was administered in addition to the calcitonin. Partial relief of the symptoms occurred. Throughout this period the patient's Paget's disease remained clinically and biochemically quiescent (Fig. 1). From our observations in this patient, it seems unlikely that CT exerts any significant prophylactic anti-inflammatory effect in rheumatoid arthritis. CT might, however, prevent the development of oesteoporosis that can occur in patients with rheumatoid arthritis.

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The binding of phenothiazines and related compounds to human serum albumin

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In a recent publication (Sharples, 1976) it has been concluded from measurements of R_m values, binding constants and charge transfer complexation constants that the binding phenomenon following the interaction of albumin and a series of phenothiazines and imipramines is the result of predominantly electronic rather than hydrophobic interactions. We believe that problems arising from experimental design and interpretation cast serious doubts on the validity of these conclusions. The hydrophobicity of the molecules was determined by a reversed phase thin-layer chromatographic technique using liquid paraffin on a silica gel support and developing with a mixture of 9 parts acetone and 1 part water. In investigations (Mercier, 1968) using paraffin and methanol–water mixtures as the solvent system to determine R_m values by a reversed phase chromatographic technique, silica gel was found to be an unsatisfactory support phase for phenothiazines because of the strong adsorption of the drugs onto this support. Kieselguhr and cellulose were found to be more suitable. When partition coefficients or R_m values are to be correlated with binding constants for drug-albumin complexes it is preferable to make measurements using buffers or aqueous solutions containing as low a concentration as is possible of a water miscible organic solvent. (Tomlinson, 1975). We have measured the R_m values of a series of phenothiazines using oleyl alcohol, and aqueous methanol with Kieselguhr as a support phase (Hulshoff & Perrin, 1976). R_m values for the molecules were plotted as a function of methanol concentration to obtain the R_m^- value at zero methanol concentration. The lines for the various phenothiazines are not parallel and can cross at higher methanol concentrations. Similar observations using the apolar silicone oil and acetone–water mixtures for steroids (Biagi, Barbaro & others, 1975 a), penicillins (Biagi, Barbaro & others, 1969), phenols (Biagi, Gandolfi & others, 1975 b), as well as for phenothiazines (Guerra, Barbaro & Biagi, 1972) have been made, the lines frequently crossing at acetone concentrations of 60–70%. This means that at high co-solvent concentrations R_m values can be obtained which do not agree with expected hydrophobicities of the molecules under investigation. Sharples, using 90% acetone in his investigations, shows

* Correspondence.

several pairs of drugs e.g. promazine and chlorpromazine, prochlorperazine and trifluperazine, and imipramine and trimipramine having R_m values contrary to their expected hydrophobicities. We have tried to correlate R_m values of Sharples with those of Mercier & Dumont (1969) for six of the molecules investigated by both authors. The R_{mo} values of Mercier are those extrapolated to zero methanol concentration. The derived equation is then:

$$R_m 90\%\text{ acetone} = -0{\cdot}077\ R_{mo} + 0{\cdot}246 \quad n = 6$$
$$r = 0{\cdot}121 \quad s = 0{\cdot}295$$

Thus no significant correlation is obtained. It should also be pointed out that Sharples measured R_m values of the free bases. The molecules concerned have pKa's varying by as much as two pKa units (Green, 1967), however no corrections for the state of ionization of the molecules was made in any of the attempted correlations.

R_m 90% acetone values reported by Sharples do not conform with those which are usually accepted as a measure of the hydrophobicity of molecules and he obtains no significant correlation between these values and the albumin binding constants. He then attempts to correlate the drug albumin binding constants with binding constants for the interactions of the drugs with riboflavin in a phosphate buffer. These are referred to as charge transfer complexes. Such complexes are normally associated with the appearance of new absorption bands, and are usually measured in apolar solvents to minimize complications by solvent-solute interactions (Beukers & Szent-Györgyi, 1962). Flavins have been shown to form complexes with a range of electron-donating molecules including phenothiazines, however, little direct evidence in the form of new absorption bands has been presented (Shifrin, 1973). Indeed Yagi, Ozawa & Nagatsu (1959) who first reported the fluorescence quenching of flavin adenine dinucleotide by chlorpromazine in a phosphate buffer made no claims about the formation of a charge transfer complex. They, like Sharples, presented no evidence for the existence of such a complex, possibly because any new absorption band would be difficult to detect in an aqueous system. In investigations of charge transfer complexes using tetracyanoethylene as an electron acceptor and arylmethylcarbamates (Hetnarski & O'Brien, 1975) and phenothiazines (Mercier & Dumont, 1972) in chlorinated hydrocarbon solvents as electron donors, it was found that as the Hammett σ constant was increased following substitution in the donors, then the charge transfer complexation constant decreased. Sharples, from the measurements of the fluorescence quenching of riboflavin by the phenothiazines and related compounds in the phosphate buffer, found an increase in complex formation with increased electronegativity, e.g. chlorpromazine and promazine, and chlorimipramine and imipramine. Such an increase in binding constants is to be expected when a chlorine atom is introduced into the ring if a hydrophobic phenomenon is dominant.

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