addition radiotherapy offers useful palliation, especially where a solitary metastasis in a lung is producing haemoptyses.

Radioiodine is used in those patients whose metastases take on function after total thyroidectomy. It may prolong life and greatly increase the patient's sense of well being. Probably not more than 15 per cent. of all patients with carcinoma of the thyroid gland seen at the present time are capable of being treated in this manner.

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A very large number of articles has appeared on the subject of thyroid carcinoma in the last few years, and the references given below are not intended in any way to be a comprehensive list. The aim has been to give some of the more important contributions to thyroid literature which will serve as a guide to anyone wishing to discover more about this subject. The most useful general accounts will be found in 'The Thyroid Gland' by J. H. Means, 1948; 'Practical Aspects of Thyroid Disease' by G. Crile, 1949; and the section on the thyroid in the 'Proceedings of the National Cancer Conference' held at Memphis in 1949.

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ANNOTATION

The Phosphatases

Alkaline Phosphatase

In 1923 Dr. R. Robison, of the Lister Institute, London, began a series of experiments on the phosphatase enzyme of bone, which has led to a clearer conception of the process of bone formation and a better understanding of the mechanism of calcium and phosphate deposition. The enzyme, which is shown to be present in bone and ossifying cartilage, can be extracted by breaking up the bone and treating with chloroform water. This extract, added to a solution of a primary ester of phosphoric acid, will liberate phosphorus from its organic

combination: and in the presence of inorganic calcium the liberated phosphate is deposited as calcium phosphate. Robison suggested that the bone enzyme in the hypertrophic cells of the tissue where calcification takes place liberates free phosphate from the organic esters of phosphorus contained in the fluids bathing the bone and cartilage, thus giving a local increase of the amount of inorganic phosphate in solution. According to the law of mass action any increase in the concentration of phosphate ion will, in the presence of the ionic calcium of the plasma, lead to a deposition of bone salt. This bone enzyme phosphatase is invariably present in bone or ossifying cartilage, while unossifying cartilage fails to show any phosphatase activity. Young, rapidly-growing

bones have much more of the enzyme than older or adult bone; while the bones of rachitic children and animals have considerably more than those of normal children of the same age.

In addition to being present in bone, phosphatase also occurs in the blood. Plasma of normal individuals contains a small amount of phosphatase corresponding to about 5-10 phosphatase units per 100 ml.—the arbitrary term in which it is the custom to express the amount of the enzyme. It was shown by Kay (1931) that in conditions of generalized bone disease the phosphatase seems to leak out of the bone into the blood and to accumulate there in large amounts. As a consequence, it is of considerable diagnostic value to determine its concentration in the serum or plasma of persons suffering from rickets, osteomalacia, Paget's disease, von Recklinghausen's disease (osteitis fibrosa cystica) and also in many cases of malignant bone disease. In this regard the papers by Franseen, Simmonds and MacLean (1939) and the review which appeared in this journal by King and Delory (1948) are useful summaries of the results obtained.

Children have more of the enzyme in the plasma than adults. Gray and Carter (1949) give the average value as 17 units per 100 ml., and the range as 7-20 units. The phosphatase in 54 cases of clinical rickets fell for the most part between 25 and 40 units per 100 ml., with an extreme range of 76 units. In early rickets, with symptoms but no signs, the average value of 35 units per 100 ml. In osteomalacia, Paget's disease and von Recklinghausen's disease values between 20 and 80 units per 100 ml. are frequently encountered, and figures greater than 100 units are not uncommon.

In addition to its place in the study of bone disease, estimation of the enzyme may also be usefully employed in the differential diagnosis of jaundice. Roberts (1930) showed that a marked accumulation of the enzyme takes place in the serum in cases of obstructive jaundice. Armstrong, King and Harris (1934) and Bodansky and Jaffe (1934) demonstrated an enormous increase in the amount of the enzyme in the plasma of dogs in whom experimental obstructive jaundice had been produced by ligating the common bile duct. On release of the obstruction, the concentration of the

enzyme in the blood returned slowly to normal. In experimental toxic jaundice the rise was not so marked, and in haemolytic jaundice the enzyme did not increase above the normal limit. In man the concentrations of phosphatase encountered clinically are fully set out by Herbert (1935), and discussed by Cantarrow and Nelson (1937), and Sherlock (1946). The relation of alkaline phosphatase to other tests of liver function is fully discussed by MacLagan (1947), Sherlock (1946), and King (1949). The plasma of normal persons has 10 or less units per 100 ml. and this value is not exceeded in cases of haemolytic jaundice. Cases of infective and toxic jaundice, and of obstructive jaundice, where the obstruction is intermittent or only partial, show values above normal, which usually lie between 10 and 30 units per 100 ml. In obstructive jaundice, where the obstruction is complete or of long standing, the plasma phosphatase may be very greatly increased. Values above 30 units per 100 ml. are usually encountered, and sometimes they may be over 100 and even as high as 200 units per 100 ml.

The amount of the alkaline phosphatase is measured in the plasma by determining the amount of hydrolysis which takes place when the enzyme in a measured amount of plasma is allowed to act on a suitable substrate, i.e. an ester of phosphoric acid such as glycerophosphate or phenylphosphate, under standard conditions of temperature, alkaline pH (9 to 10) and time. The amount of phosphate or phenol set free is taken as a measure of the amount of enzyme present. Well known methods of estimating phosphatase are those of Jenner and Kay (1932), King and Armstrong (1934) and Bodansky (1933). The King-Armstrong method and units of phosphatase are most commonly used in this country. This and the Jenner and Kay procedure yield almost equal results. The methods are described in King's 'Micro-analysis in Medical Biochemistry' (1951).

Acid Phosphatase

In addition to the alkaline phosphatase mentioned above, there is an acid phosphatase which is pretty well confined to the prostate gland, but which also occurs in small amounts in the blood plasma. Unlike bone phosphatase, this enzyme

is optimally active at an acid reaction, namely, a pH of 5. In prostatic conditions, particularly in carcinoma of the prostate with secondaries in the bone, large amounts of the enzyme are found in the plasma, coming in part from the prostate and in part from the secondary growths in the bone. Normally there are 1-3 acid phosphatase units per 100 ml. of plasma. In carcinoma of the prostate with secondaries in the bone values above 5 units per 100 ml. and up to 30 units per 100 ml. are commonly encountered, and in occasional cases 100 or even more units of the enzyme may be found per 100 ml.

This enzyme has been used extensively in the investigation of prostatic disease, and has been particularly investigated by Gutman and Gutman (1938), Huggins *et al.* (1941), Watkinson *et al.* (1944), and the results have been reviewed by King

and Delory (1948). Not only is acid phosphatase a very useful diagnostic adjunct in the study of prostatic carcinoma, but it may also be used with great advantage in following the effects of stilboestrol therapy.

Because of the great difference in the pH at which these two phosphatases act optimally, it is possible to estimate one in the presence of the other. The same substrate is used for both, but different buffers are employed; and it is merely necessary to allow the enzyme to act on its substrate at the characteristic pH of 5 for acid phosphatase and 10 for the alkaline one. The estimations are simple, quick and easily executed, and their use has become routine practice in all modern biochemical laboratories attached to hospitals.

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