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Bone and Toxic Minerals

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During the years between the wars, we have seen the development of the spectrograph and of sensitive colorimetric methods for the identification and determination of elements in biological materials. As a result it has been established that animal and human tissues contain elements whose existence in the tissues had not previously been recognized. The concentration of these elements is low in comparison with that of such elements as sodium and potassium. It is quite possible that, if more sensitive methods could be devised, other elements would be recognized in even more minute concentrations.

It is of some interest to consider the reasons stimulating such work. In certain instances it was simply a desire to determine the maximum number of elements, even in low concentration, in animal and human tissues. At the same time our knowledge of the nutritional requirements of the animal body was being extended. During this period it was established that copper was a constant constituent of animal tissues and, although present in low concentration, was an essential element. Increased interest was also being taken in industrial toxicology. It became necessary to develop more sensitive and reliable methods for the identification and determination of toxic elements in excreta and in tissues.

Certain of these elements occur constantly, whereas others are found only spasmodically. Elements such as copper and zinc have been shown to be essential for normal animal and human metabolism. Lead, arsenic and fluorine, elements known for their toxic properties, are present in normal animal and human tissues. There are elements now known to be present in tissues in low concentration, which, in the present state of our knowledge, are without function. These elements are derived almost entirely from foodstuffs.

Certain toxic elements are deposited in the skeleton in preference to the soft tissues. Of these, fluorine, lead and radioactive metals of high molecular weight have received most attention.

Radioactive metals

The continued absorption of radioactive metals of high molecular weight has a cumulative effect, resulting in increasing concentrations in the skeleton. The effect of the radiations is disastrous. The continual bombardment of the bone marrow results in a profound and leukopenic anaemia. In addition, both the upper and lower jaws develop destructive lesions similar to those seen in phosphorus poisoning and due, as in that disease, to bacterial infection from the mouth superimposed on a specific osteitis. There has been comparatively little metabolic work carried out in this condition. Work in this field has been mainly of a preventive nature.

Fluorine

Fluorides occur in small amounts in the normal diet and in drinking water. Small quantities occur in normal tissues, the highest concentrations being found in the skeleton. There is no certain evidence that the small quantities of fluoride in normal tissues exert any essential function. There is some evidence, however, that, when optimal amounts of fluoride are available during growth, there is increased resistance to dental caries.

A moderate excess of fluoride results in dental fluorosis—an unsightly mottling of the teeth. Great excess of fluoride, which can be derived from drinking water, results in gross skeletal changes with severe disabilities and sometimes death. Such pathological changes are permanent. It has been demonstrated that the fluoride content of bone increases with age (Murray & Wilson, 1946). Comparatively little metabolic work has been carried out on subjects in this condition. Work in this field has been mainly of a preventive nature.

Lead

The factors influencing the absorption and distribution of lead in the animal body have received relatively more attention. There are several reasons to account for this. Lead poisoning has been on a very much wider scale, especially in industry. Lead poisoning is not usually a fatal condition and, with successful clinical treatment, the body is not subject to permanent pathological change. Since lead poisoning may respond successfully to treatment, the condition has received much attention not only from the biochemist, but from the clinician. We are indebted to Aub, Minot, Fairhall & Reznikoff (1926) for much of the earlier work on the metabolism of lead.

Lead is present in measurable quantities in 'normal' tissues (Table 1). These are derived almost entirely from the diet, which supplies daily about 0·5 mg. Lead tends to be deposited preferentially in the skeleton. Bones such as femur and tibia, however, tend to contain higher concentrations than rib or vertebra. It has been observed that

Table 1. *Lead content of 'normal' human tissues*

(Tompsett & Anderson, 1935; Tompsett, 1936). The figures are expressed in mg Pb/kg fresh tissue)

Soft tissues		Bones	
Liver	0·9–4·6	Rib	5·0–12·9
Kidney	0·7–3·7	Vertebra	2·6–14·7
Spleen	0·4–5·9	Femur	18·2–108
Brain	0·2–0·7	Tibia	15·3–96·5

Table 2. *Lead content of tissues of persons with a history of abnormal exposure to lead*

(The results are expressed in mg Pb/kg fresh tissue)

Occupation ...	Painter	Painter	Metal worker	(Condition due to contamination of drinking water with lead)
Age (years)	41	60	60	26
Liver	4·5	2·4	5·4	7·1
Kidney	1·0	2·9	2·0	4·6
Brain	1·0	—	1·4	3·1
Rib	119	22	51	52
Vertebra	19	9	13	—
Femur	—	—	51	52
Tibia	—	—	79	53

the concentration of lead in femur and tibia increases with age (Lynch, Slater & Osler, 1934; Tompsett & Anderson, 1935; Tompsett, 1936). The concentration of lead in the soft tissues and such bones as rib and vertebra is unaffected by age. Such findings suggest that, under so-called 'normal' conditions, there is a retention of lead in certain parts of the skeleton.

I have had the opportunity to examine tissues taken *post mortem* from four persons with histories of abnormal exposure to lead (Table 2). The markedly increased concentration of lead in the ribs is particularly noteworthy.

Factors influencing the distribution of lead between the soft tissues and the skeleton are of particular interest to the clinician. It is generally assumed that only lead present in the soft tissues exerts a toxic action. The 'inert' lead of the skeleton is, however, a potential danger if mobilized and passed to the soft tissues. Mobilization of lead may be assessed either by an increase in its excretion or by an increase in the level in the blood.

It would appear that the so-called 'normal' lead of the skeleton is difficult to mobilize by metabolic means. On the other hand, lead recently deposited in the skeleton as the result of abnormal exposure is relatively easily mobilized by metabolic means. Such mobilization may result in the onset of toxic symptoms. In many respects lead resembles calcium. A high-calcium diet favours deposition of lead in the skeleton, whereas a low-calcium diet, with or without parathyroid hormone therapy, has a

reverse effect. Acidosis, which can be produced clinically by the administration of ammonium chloride, also favours the release of lead from the skeleton.

Recently absorbed lead is said to be stored in the bony trabeculae and, in time, it is deposited in the cortex of the bones as the less soluble tertiary phosphate (Gant, 1938*a*, *b*). Such could account for the two different ways in which lead appears to exist in the skeleton.

The question naturally arises as to whether the lead of the skeleton, particularly that laid down under 'normal' conditions, can be mobilized as the result of disease. This applies particularly to those diseases having a gross effect on the skeleton. Brown (1946) and Tompsett (1948) have shown that mobilization of lead, as indicated by an increase in the lead in the blood, can occur in the following conditions: (1) involvement of the skeleton by malignant disease; (2) senile osteoporosis; (3) marrow hyperplasia—pernicious anaemia, leukaemia. In such persons, with no history of abnormal exposure to lead, there were no definite clinical symptoms of lead poisoning. In one group, the urinary coproporphyrin levels were determined. These levels are usually elevated in lead poisoning, but were found to be within normal limits in these special cases. The probability is that, in most cases, the release of lead from the skeleton, as the result of the above disease processes, is comparatively slow. In persons with a history of abnormal exposure to lead, the result of such diseases may however be more serious. A case of subacute lymphatic leukaemia, with a history of abnormal exposure to lead, has been reported in which symptoms of lead poisoning appear to have been precipitated by the disease (Brown & Tompsett, 1945).

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Radiology of Bones in Health and Disease

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