ALBERS-SCHÖNBERG DISEASE (MARBLE BONES)

Report of a case with a study of the chemical
and physical characteristics of the bone

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The condition called osteopetrosis by Karshner (1926) was first described accurately by Albers-Schönberg (1904), and in a subsequent article (1907), on the basis of the radiographic appearance, he likened the bones to marble. That the condition is commonly referred to eponymously emphasises the lack of precise information about the mechanical abnormalities resulting from the striking physical peculiarities of these bones. Indeed, not only are there very few records of investigations made at necropsy into these abnormalities, but there is also considerable divergence of the opinions expressed by surgeons on the characteristics of the bones at operation. Two of these opinions may be given to exemplify this divergence. On the one hand Henderson (1928) stated that the bones are "so hard that they break the edges of chisels and drills." On the other hand Pirie (1930) found that the amount of penetration of a normal bone that could be achieved by twenty-three turns of a certain drill required only seven turns in a case of this disease. The most recent review of Albers-Schönberg’s disease was that of Fairbank (1951), which included seven personal case reports. He stated that all cases show abnormal bone density to x-rays and that, although a tendency to an excessive number of fractures may be present, "on the whole the fragility of the bones has been much exaggerated."

This is a rare disease and, so far as can be discovered, the case reported here is the first that has come to post-mortem at Guy's Hospital—an incidence of the order of one in 10,000 hospital necropsies. The case afforded the opportunity to investigate the exact nature of the physical and chemical abnormalities of the bones and the resulting observations are the subject of this paper. Fairbank's (1951) comprehensive account has been taken as the basis for the diagnosis and it may be said at once that this patient conforms well with his description.

CASE REPORT

A woman aged forty-one was admitted to the neurosurgical unit of Guy's Hospital, under Mr Murray Falconer, for the treatment of a subarachnoid haemorrhage. She had had three verified attacks of the same condition in the three weeks before admission. During the fourth attack she developed a right hemiparesis and died in coma.

During the previous two years she had several times a day felt numbness in the left side of the face and head which she described as "coldness and pins and needles." She had always required especially large hats; there was no history of fractures. Her father died of a "tumour of the head" but there was no evidence of bone disease in the other two members of the family who have been traced.

On examination at the time of admission, abnormal neurological signs were found which, since they changed their character while under observation, were almost certainly due to haemorrhage. Gross myopia (8-9 dioptres) was present but there was no optic atrophy or deafness. Radiographs showed increased bone density in the proximal ends of the femora and tibiae and particularly marked changes in the skull. So dense was the skull that few cranial details and no vascular pattern at all could be seen after right carotid arteriography. Investigations—A blood count made three weeks before admission showed the following:
haemoglobin 72 per cent (11 grammes per cent); red blood corpuscles 4,150,000 per cubic millimetre; white cells 15,400 per cubic millimetre (neutrophils 80 per cent, myelocytes 3 per cent, lymphocytes 15 per cent, monocytes 1 per cent, basophils 1 per cent). Thus there was mild anaemia, a slight neutrophil leucocytosis and a few myelocytes; but no primitive white cells were found in any subsequent investigation. Apart from the myelocytes the count was consistent with the history of repeated subarachnoid haemorrhages.

Necropsy was performed twenty hours after death. The body was that of a well nourished woman of small stature (height: 4 feet 11 inches [150 centimetres]) with an exceptionally large head. Bilateral basal broncho-pneumonia was present and there was a benign left ovarian teratoma. The parathyroid glands were normal (combined weight 142 milligrams). No evidence of extramedullary haemopoiesis was found and the other organs were normal.

The brain itself was normal but there was a large haemorrhage into the left lateral and the third ventricles arising from a ruptured berry aneurysm at the divergence of the left anterior and middle cerebral arteries. The haemorrhage had extended into the pituitary fossa. A similar but smaller aneurysm was present on the right. A further congenital anomaly of the intracranial vessels was reduplication of the left posterior communicating artery (Fig. 1).

The skeletal abnormalities were widespread and variable. The calvaria was enormously thickened (mean thickness 1-7 centimetres) and showed no differentiation into inner and outer tables, being composed of compact bone throughout. In consequence it was very heavy, weighing 1,208 grammes (mean weight of five normal adult female calvaria cut similarly was 302 grammes). The cranial cavity was not diminished, the increase in size of the head being due solely to external thickening of the skull. The dura separated normally. All the normal prominences inside the skull were greatly hypertrophied but there was no foraminal narrowing; for example the right optic foramen measured five by six millimetres. There were no air spaces in the mastoid parts of the temporal bones but there were some small ones, about three millimetres in diameter, in the sphenoid bone. One of each of the long bones was examined and all showed similar changes. The cortices were thickened, and thickening of the trabeculae gave a coarse medullary pattern. The cortical changes were most marked at the middle of the humerus, tibia and femur (mean thicknesses seven, seven and ten millimetres respectively) and the abnormal medullary pattern in the lowest third of the humerus (Figs. 2 and 3). There was very little marrow in the long bones, but the vertebral bodies, apart from the trabecular pattern, looked normal.

Histological examination—The unruptured smaller aneurysm had a thin wall composed of endothelium-lined fibrous tissue only. At the margin of the sac the media and intima of the artery disappeared, the elastica about a millimetre before the rest, so that the adventitia alone formed the wall of the dilation. The haemorrhage into the pituitary fossa had invaded the gland so that only about half of the anterior lobe tissue remained. A small parapituitary epithelial rest or "adamintoma" was present. The parathyroid glands were of predominantly chief cell type and the pancreatic islets were abnormally numerous and large. No evidence of extramedullary haemopoiesis was seen.

The bones showed coarse trabeculation (Fig. 4) with little cellular evidence of osteoblastic or osteoclastic activity, although this was probably within normal limits. As far as could be
Subcortical marrow of upper end of tibia (H. and E. × 12).
judged from sections that required prolonged decalcification there was no abnormality of haemopoiesis. Section of the lower part of the tibia at the point where the cortex narrowed to normal width did not show any advancing edge of the pathological process.

The ovarian tumour was a benign teratoma showing elements derived from all three germinial layers (hairs, columnar cells similar to those found in intestinal epithelium, and bone). "Chemical investigations"—These were made on dried turnings of cortical bone. The findings are shown in Table I. As they all fall within accepted normal ranges the methods are not described but references to them are given in the footnotes to the Table.

### TABLE I

<table>
<thead>
<tr>
<th>Chemical Composition of the Bones</th>
<th>Weight per cent of dry bone</th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Normal femur</td>
<td>Normal tibia</td>
<td>Patient's femur</td>
<td>Patient's tibia</td>
<td>Patient's skull</td>
</tr>
<tr>
<td>Calcium (as Ca)</td>
<td>25.8</td>
<td>25.8</td>
<td>25.3</td>
<td>26.3</td>
<td>25.9</td>
</tr>
<tr>
<td>Phosphorus (as PO₄)</td>
<td>33.7</td>
<td>34.0</td>
<td>34.9</td>
<td>34.2</td>
<td>35.0</td>
</tr>
<tr>
<td>Carbonate (as CO₃)</td>
<td>4.1</td>
<td>4.9</td>
<td>4.3</td>
<td>4.9</td>
<td>4.9</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>4.3</td>
<td>4.3</td>
<td>3.7</td>
<td>4.2</td>
<td>4.3</td>
</tr>
<tr>
<td>Hydroxyproline*</td>
<td>—</td>
<td>3.15</td>
<td>—</td>
<td>3.13</td>
<td>—</td>
</tr>
<tr>
<td>Collagen</td>
<td>23.3</td>
<td>23.2</td>
<td>23.4</td>
<td>23.6</td>
<td>24.9</td>
</tr>
<tr>
<td><em>Mean of results calculated from N and hydroxyproline contents</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight per cent of collagen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrosine†</td>
<td>—</td>
<td>1.28</td>
<td>—</td>
<td>1.23</td>
<td>—</td>
</tr>
</tbody>
</table>

* Neuman and Logan 1950. † Rogers, Weidmann and Parkinson 1952.

**Physical investigations**—Measurements were made, on isolated cortical bone, of the specific gravity, Young's modulus of elasticity, and breaking strength; the resistance of the bone surface to a standard penetrating force was also determined.

For the first three measurements, rods of bone were turned on a lathe from strips sawn from the cortex of the upper end of the femur on its medial aspect just below the neck, from the crest of the tibia just below the epiphysial line, and from the right frontal bone just anterior to the fronto-parietal suture two centimetres above and parallel to the supra-orbital ridge. Two skull specimens were examined: one taken from bone macerated in 10 per cent caustic soda for two months, and one from untreated bone. The rods were about four centimetres long and were 0.358 centimetres in diameter giving a circular cross-section of 0.1 square centimetres. Six controls from patients of similar age were examined, in none of whom was the cause of death likely to have caused any bony abnormality. The first was prepared from a femur but it was found simpler to obtain subsequent specimens from the tibial crest. Normal skulls were found to contain insufficient compact bone to permit turning of similar rods and the same was true of a case of hyperostosis frontalis interna. All bones examined had been preserved in 4 per cent formaldehyde.

The specific gravity was calculated from data obtained by measuring the lengths of the pieces, calculating their volumes, and subsequently weighing them.

The other measurements were made by applying weights to the central point of a bone peg suspended in a brass cradle of 2.86 centimetres internal diameter. A counterpoised arm
in contact with a recording device allowed measurements of deflection to be made (Figs. 5 and 6). Young's modulus, or the modulus of longitudinal elasticity, was obtained by plotting these deflections against the weights causing them; it was found that they invariably formed a straight line right up to the point at which fracture occurred (Fig. 7). From the graphs so obtained the mean deflection for a unit weight was obtained and the Modulus, $E$, was calculated from the formula: 

$$E = \frac{W^2}{12r^4}\times\frac{I}{d}$$

dynes per square centimetre, when $l$ is the length of the peg within the cradle, $r$ its radius and $d$ the amount of depression caused by the addition of a force $W$ dynes.

A simpler apparatus was used for the measurement of breaking stresses. It was composed of a circular platform ten centimetres across soldered on to a tapered brass rod one centimetre in diameter that ran through a loosely fitting tube held vertically in a burette clamp (Fig. 8). The tip of the rod was allowed to rest on a bone peg suspended in the same cradle as before and half-kilogram weights were added to the platform one at a time until the rod broke. Histological sections were cut transversely close to the fractured surface to confirm that the long axis of the peg was along the Haversian systems, and counts were made of their number in each peg (Table III).

The penetration caused by applying a weight of 10 kilograms to a hard steel needle—the point, which formed an angle of 60 degrees, resting on the surface of a bone—was measured in the large apparatus; care was taken to avoid errors from elastic compression.
TABLE II

Physical Characteristics of the Bones

<table>
<thead>
<tr>
<th>Source of compact bone</th>
<th>Young's modulus × 10</th>
<th>Breaking point in kilograms</th>
<th>Penetration in centimetres caused by a weight of 10 kilograms</th>
<th>Specific gravity</th>
</tr>
</thead>
</table>
| Normal tibia (5 specimens) | 9·8  
(s.d. ±1·2) | 13·8  
(s.d. ±2·2) | 0·05  
(s.d. ±0·003) | 1·46  
(s.d. ±0·18) |
| Normal femur (1 specimen) | 11·2                | 18·0                      | 0·04                                                        |
| Normal skull (2 specimens) |                     |                           |                                                             |
| Patient's tibia . . . . | 13·7                | 21·0                      | 0·06                                                        |
| Patient's femur . . . . | 13·4                | 18·0                      | 0·07                                                        |
| Patient's skull:  
not macerated . . . . | 9·6                 | 10·0                      | 0·03                                                        |
| macerated . . . .     | 6·0                 | 7·0                       | 1·72                                                        |

TABLE III

Number and Disposition of the Haversian Systems Seen in Histological Sections of the Bone Pegs on which the Physical Measurements Were Made

<table>
<thead>
<tr>
<th>Source of compact bone</th>
<th>Number of Haversian systems per square centimetre</th>
<th>Number cut transversely</th>
<th>Number cut obliquely</th>
</tr>
</thead>
</table>
| Normal tibia           | 920  
(s.d. ±134) | 880  | 40  |
| Patient’s tibia        | 1090   | 1080 | 10  |
| Patient’s skull        | 340    | 230  | 110 |

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RESULTS

The results are summarised in Table II. The readings for the one specimen of normal femur investigated come within the range for the five specimens of normal tibiae, so that this range may be taken to represent the behaviour of normal long bone cortex. The values for the abnormal femur and tibia are likewise similar and will be considered together. Those for the skull, before and after maceration, although interesting, are quite different from any of the other results. This is what might be expected from the nature of the stresses to which this part of the skeleton is liable and is reflected by the appearance of the cross-sections of the rods (Table III). These show that whereas the Haversian systems of the normal and abnormal long bones are arranged similarly and are mostly parallel to each other, they are much less regular in the pathological compact bone of the abnormal skull.

If the values for normal and abnormal long bone cortex given in Table II are compared it is seen that the abnormal bone is more rigid (that is, it has a greater modulus of elasticity) than the normal and that this difference exceeds conventional limits of significance. In keeping with this, but in contradiction to much current surgical opinion, the force required to break abnormal tibial bone was greater than that needed for the normal, but the breaking stresses for the abnormal and normal femora were the same. The readings are few and the observed differences not great enough to establish the existence of any definite difference in behaviour, but they do at least make it certain that in this patient, who had no history of fractures, the bone fragility was not increased. Maceration of the skull greatly increased the ease with which the frontal bone pegs bent and fractured (if the samples were comparable).

The standard penetration test applied also revealed significant abnormalities. There was no difference between the values for normal skull and normal tibia but marked differences were present in the comparable values for the abnormal bones. The calvarium resisted penetration but the long bones, both of which behaved similarly, were more easily entered by the needle.

The specific gravity of all the abnormal bones was considerably greater than the normal mean, and that of the long bones was significantly outside the normal range.

DISCUSSION

There can be no reasonable doubt that this patient had Albers-Schönberg's disease. Although there was no history of fractures and no family history, the disease had been present for a very long time and probably from early childhood. The age (forty-one years) of death does not diminish the probability that this is the correct diagnosis, for in a series of twenty-nine cases (Nussey 1938, Fairbank 1951) eight patients were over forty and only fifteen were children. Necropsy revealed no other cause for bone disease and showed numerous features entirely consistent with the diagnosis made. In addition several congenital abnormalities (multiple intracranial berry aneurysms, a parapituitary epithelial rest and a benign ovarian teratoma) are perhaps further evidence that the condition of this patient's bones was the result of a developmental error. It may then be concluded that the case has been correctly diagnosed.

The physical characteristics of the abnormal bone are the most interesting of the findings and it is thought that they may have a bearing upon the differences of opinion that have long existed about this disease. Their main characteristic is the marked contrast between the values for skull and long bones which, in general, fall on opposite sides of the mean values for the normal tibia. The only exception is the specific gravity, all the marble bones being denser than the mean for the normal tibia. Despite this the difference between skull and long bones is still apparent, for whereas the former falls within the normal range that of the latter is outside its upper limit. The skull is thus harder than normal and bends and breaks more easily, whereas the long bones are softer and more resilient and resistant to fracture. Although
not all of these deviations are significant they do suggest that the changes in the bones in this condition are of a patchy distribution, a finding which accords with the radiographic appearances in this and other cases. Although the data presented here relate only to the strength of the bones in the various anatomical sites in one quiescent case at the time of death, it is at least possible that these changes also varied in distribution during the course of the disease. Thus it may well be that younger patients have more of the fragile type of bone and less of the stronger kind, the proportion of the latter increasing as age advances.

It seems more probable in this case, however, that the behaviour of the bone in these mechanical tests was related to the functions that they usually performed and, through these, to the arrangement of the Haversian systems in the compact bone. Thus the bone most resistant to fracture was from the thickened tibial cortex and the least resistant was from the abnormal cortical bone of the skull. The former was constantly subjected to longitudinal stresses and the lacunae were mostly parallel to each other, whereas in the latter these stresses were minimal and the arrangement of the lacunae was more haphazard.

The greater specific gravity of the abnormal bones is probably related to the size of the Haversian canals, which appear in the sections to be somewhat smaller than normal. The specific gravity did not correlate well with either penetration or breaking point but it did with the estimates of Young's modulus. The latter also correlated quite well with the measurements of penetration and the breaking point determinations (Fig. 9), a fact which suggests that the simpler method is probably quite as useful for the investigation of future cases as the more elaborate determinations of Young's modulus.

The marked change in behaviour of the compact bone of the skull after maceration suggests that the strength of the bone depends partly upon its collagen content. The nitrogen analysis of these bones showed that this was normal and the hydroxyproline and tyrosine analyses of both normal and abnormal tibiae supported this. Collagens are unusual among proteins in containing 13 to 14 per cent of hydroxyproline (Neuman and Logan 1950) and less than 1 per cent of tyrosine (Neuman 1949). Determinations of the former amino-acid are considered specific for collagen and the presence of more than 1 per cent of tyrosine in bone collagen indicates the presence of a small amount of non-collagenous protein (Rogers, Weidmann and Parkinson 1952). That all analyses of these bones were normal, even in this last important detail, suggests that the disease is due to a micro-structural defect, not to anomalous bone metabolism, and the histological findings support this conclusion. It cannot therefore be claimed that any new light has been thrown on the pathogenesis of the disease.

In view of these results osteopetrosis is no more acceptable as a name for this condition than is marble-bone disease, the latter having historical priority as well as being a fairly accurate description of the naked-eye appearances. Nor would another name based upon the radiographic appearances be preferable, for there are other causes of increased opacity to x-rays, and it would be hard to find a single word that would describe the variable behaviour of these bones under stress. Until the underlying abnormality of osteogenesis has been discovered it may therefore be as well to continue to describe the disease either by the eponymous title of Albers-Schönberg's disease, or by the descriptive one of marble bone disease, according to the preference of the user.

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SUMMARY

1. A case is described of the marble bone disease of Albers-Schönberg in a woman of forty-one who died from subarachnoid haemorrhage. Several congenital abnormalities were present.
2. No significant abnormality of the chemical composition of the bones was discovered.
3. The long bones were more resilient, stronger, softer and of higher specific gravity than normal and the abnormal compact bone of the skull was less resilient, weaker, harder and of about the same density as normal bones.
4. The simple investigation of determining the breaking strength of cortical bone yielded results similar to the more complex investigations and if applied to a larger series of cases could provide sound data on which to base speculations about this condition.

I wish to thank Mr Murray A. Falconer, Director of the Neurosurgical Unit, for permission to use the case records, and Professor G. Payling Wright who suggested the investigation. I am also most grateful to Dr W. H. H. Merivale, Reader in Clinical Pathology, Dr M. V. Stack, of the Department of Dental Medicine, and Dr I. Macdonald, of the Department of Physiology, who kindly undertook the chemical estimations and interpreted the results. The apparatus for measurement of strain was designed by Dr Macdonald.

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