ties of the bones become the site of haematopoietic tissue, and in the higher vertebrates bone is known to act as a storehouse of mineral salts.

In its finer structure, too, bone shows a progressive evolutionary change, although here the account is far from complete. In the earliest vertebrates the bone is acellular. In the primitive bony fishes the bone is cellular, although the arrangement of the lacunae is very irregular, and the osteocytes do not long survive. In the advanced bony fishes the trend has been once more toward the acellular condition, but terrestrial vertebrates show a trend toward greater regularity, longer survival of the osteocytes, and the appearance of nutrient canals and secondary bone arranged in Haversian systems. These trends reach their culmination in the bone tissue of modern mammals. There is, however, some reason to believe that some of the most ancient fish-like vertebrates had also a very regular type of cellular arrangement.

Knowledge is lacking of the histology of bone in many extinct vertebrate groups, but the fact that bone structure is known to vary so greatly between the different groups studied suggests that this knowledge would be well worth having. Even less is known about the reasons underlying this variation. The problem of correlating the evolution of bone structure with that of bone function remains one for the future.

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Bone as a Skeletal Structure

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Bone has provided absorbing problems for biologists for many hundreds of years. A fascinating account of the early history of this subject is to be found in *Menders of the Maimed* by Sir Arthur Keith (1919), a new edition of which is to be published shortly. The point of interest has varied from time to time but the basic problem is still the properties of bone as a supporting structure; this is the practical aspect of bone physiology which is most obvious to the man with a fractured femur, or to the surgeon who looks after him. I reviewed the information, such as it is, on the healing of bone some years ago (Bell, 1945) and I propose to confine my attention here to what might be termed engineering problems. These are, firstly, the search for the factors determining the shape of a bone and, secondly, the measurement of the physical properties of bones.

In the embryo the earliest cartilaginous rudiments possess the characteristic shape of the future bone, for example the head, trochanter and condyles of the femur can be recognized; furthermore, femora removed from $5\frac{1}{2}$- and 6-day-old chick embryos, and

grown by tissue-culture methods, increase to several times their original length and yet still maintain their characteristic shape (Fell & Robison, 1929). Since in tissue culture factors such as the weight of the embryo, muscle pull, relationship with other tissues and the circulation are absent, there is no doubt that the general form of a bone is to some extent under the control of intrinsic factors. This power of self-differentiation, picturesquely described by John Hunter as a form of consciousness, is still present to a remarkable degree in the human infant after birth. For example, the fragments in a birth fracture of the femur are usually firmly united in 2 or 3 weeks and even if union takes place with the fragments overlapping at right angles the process of remodelling is carried out so efficiently that in less than a year the radiologist finds it difficult to decide whether the right or left femur had been fractured (White, 1944). Even in older children it is remarkable how deformities after fracture eventually disappear.

There is no lack of evidence, however, that the final form of the bone is influenced by factors external to it. In a case of acute osteitis of the radius the bone may have to be removed; the graft from the tibia put in its place quite soon takes on the typical appearance of the radius with a normal medullary cavity (White, 1944). Muscle function undoubtedly has an effect on the shape of the bones. Ross (1950) has reported the case of a labourer who lost all the fingers of the right hand except the little finger. Thirty years later he had a very powerful little finger with great increase in the thickness of the metacarpal bone and of the phalanges. The size of the jaw bones is influenced by the physical composition of the diet. On a rough diet requiring considerable mastication the mandibles of rats are heavier and thicker, especially at the areas of muscular attachment, than they are on a soft pappy diet (Watt & Williams, 1951). The characteristic triangular cross-section of the tibia is due partly to the pressure on it of the anterior tibial muscles. If these muscles are atrophied the tibia has a rounded cross-section like that of the foetal bone (Murray, 1936). We may have here a conflict between extrinsic and intrinsic forces; the intrinsic forces tend to produce a rounded section which might be more efficient structurally, but the extrinsic forces modify this to the angular shape. Washburn (1947) investigated the effect of the muscle pull on the mandible by removing one temporal muscle from newborn rats. Between 3 and 5 months later the coronoid process of the mandible was completely resorbed although at birth it was well formed. The form of the skull was, however, unaffected by the loss of the temporal muscle. The relationship between the growth of the brain and the growth of the overlying brain case is quite mysterious. For example, MacDougall (1951) has described a case of a child of 4 weeks, of normal appearance, whose cranium contained only the basal nuclei and a small portion of the occipital lobes in addition to the cerebellum. The frontal and parietal lobes were one vast cyst with no evidence of increased tension. In spite of the absence of the brain, the brain case was normal. Wolffson (1950) removed various scapular muscles from rats on the 1st or 2nd day of life; the non-operated side served as control. It was found later that the shape and size of the scapula was much changed.

There is considerable evidence of nervous influences on bone growth. An obvious example is the small limb in birth palsy, or the slight diminution of the bones of the paralysed limb in cases of anterior poliomyelitis. The latter effect can be imitated

experimentally by cutting the ventral roots of the spinal cord in growing cats (Bell & Robertson, 1946). These lesions are, however, accompanied by paralysis and it may be that the loss of muscle pull, as in Washburn's (1947) and Wolffson's (1950) experiments, is even more responsible than the loss of the connexion with the nervous system for the change in size. This objection cannot, however, be sustained in the description by Penfield & Robertson (1943) of the 'comparative moderate smallness' of the contralateral part of the body in children with lesions of the postcentral gyrus, even when the precentral gyrus is normal. The alteration in size produced by such cortical lesions is, however, much smaller than that seen in spinal lesions. The atrophy following nerve section can sometimes by overridden. Wermel (1934, 1935) found that, in rats, complete or partial removal of one forearm bone was followed by an increase in the thickness of the other. No doubt this operation increased the stress on the remaining bone. This, however, is not the full explanation, since the remaining bone increased in size even when the functional activity of the limb was reduced considerably by nerve section.

The pattern of the cancellous tissue in long bones has provided the anatomist-cum-engineer with most intriguing problems. The cancellous tissue in the head of the femur is especially well developed and undoubtedly the spongiosa is distributed to resist the stresses to which the neck of the femur is subjected. The head, neck and shaft of the femur have been compared to a crane in which two stresses have to be allowed for, namely tension and pressure. An economically constructed crane is designed so that the greatest mass of material is placed where the stress is greatest. In the trajectorial theory the cancellous tissue has been picturesquely described as being a crystallization of the lines of force. If this is so, the bone tracts or trajectories of pressure and tension should cross at right angles. This is not always so, and in any case the pattern varies considerably from one specimen to the next. Jansen (1920) points out that in coxa vara, although the tension in bearing the weight of the body is greatest on the convex side of the neck, the strongest development of the spongiosa does not occur there but on the concave side where there is pressure. He believes that pressure is the adequate stimulus for bone formation. Tension in tendons, aponeuroses, fasciae and ligaments does not induce ossification. It is clear, however, from tissue-culture experiments that bone can form in the entire absence of pressure or tension. We have, moreover, no idea as to how stresses in bone act on osteoblasts or osteoclasts. Furthermore, such static considerations do not do justice to the full function of the femur. The muscles arising from bones probably apply to them greater forces than does the fraction of the weight of the body that is supported by the bone. Indeed it has been calculated (Bell, Cuthbertson & Orr, 1941) that bones are very much stronger than would be necessary if they were mere props. They have been designed by nature for much more severe stresses.

I should like to mention briefly two techniques recently applied to whole bones. The first is the method of estimating bone density painstakingly worked out by Mack, Brown & Trapp (1949) and Mack (1950, p. 30). An X-ray photograph is taken of a bone together with an ivory step wedge. From this their microphotometer can produce a graph of the amount of mineral matter at any cross-section of the bone, such as at the

hand, the foot, or the knee. They have found that the ends of a long bone, such as the femur, and also the os calcis change rapidly in density when the calcium intake is altered, whereas the phalanges are very slow to change. Here at last is a method for investigating the relation between nutrition and bone structure in man. Interesting results may be expected from the surveys which Mack is now carrying out.

The second is the stress-coat deformation technique used by Evans and his colleagues (Evans, Pedersen & Lissner, 1951). Bones from cadavers are sprayed with brittle lacquer (originally used to test aircraft structures) and are then loaded by a hydraulic testing machine. At a certain tensile strain the lacquer cracks and the cracks, when filled with indian ink, are easily photographed. It has been shown that tension is the main cause of failure, that is fracture, of bone.

If one believes that it is an advantage to possess strong bones then two problems arise—how is the strength of the bones to be measured and what are the nutritional factors likely to bring about this strength? With these questions in mind we (Bell *et al.* 1941) tried to find the effect of various levels of calcium intake on bone growth and strength. Growing albino rats were put for 2 months on a diet of constant protein, carbohydrate, fat and vitamin content but of varying calcium content. No matter whether the calcium content of the diet was very low or very high the external dimensions of the femora were almost the same. On the very low calcium intakes the bones formed had very thin walls; as the diet improved up to 0·36% calcium so did the femoral wall thicken and the marrow cavity diminish. Greater calcium consumption made no difference whatsoever to the bones. The strength of the bone measured by bending tests (Bell *et al.* 1941; Weir, Bell & Chambers, 1949) showed that, whereas the strength of the individual bones increased with increased calcium intake up to this same point, the breaking stress, which measures the quality of the material, was the same in all experiments. In other words, if one compares the shaft of the femur to a factory chimney, it appears that, on a good diet, varying only in its calcium content, the quality of the bricks throughout is of the highest and the external appearance is the same. The only variation is in the number of bricks laid down to form the thickness of the wall. The central space cannot for some unknown reason be encroached on to more than a fixed extent.

The picture is, however, very different when the basic diet is defective and especially when it is so defective that rickets is produced (Bell, Chambers & Dawson, 1947; Weir *et al.* 1949). In these experiments young rats were placed on a diet with a very abnormal calcium:phosphorus ratio (5:1). Litter-mates received the same diet supplemented with vitamin D, and other litter-mates received a good stock diet. The growth of the animals on the rachitogenic diet was very poor and the addition of vitamin D did not increase the rate of growth very much. The bone growth in the three groups, as shown by the size of the bones, varied much in the same way as the body-weight. The ash content of the bones produced on the rachitogenic diet was very low indeed (30%). The ash content was higher (40%) in those given cod-liver oil and reached its usual maximum value (60%) in those on the normal stock diet. In all instances, however, the calcium:phosphorus ratio in the ash was about 2. The individual bones on the poorest diet were much weaker and the breaking stress showed

that, on the factory-chimney analogy, the quality of the bricks was very poor. Rickets in rats can be produced only by grossly abnormal diets; from the dietary point of view rickets in dogs is more like human rickets. We examined some rachitic puppy bones kindly supplied by Lady Mellanby and found that the ash content and the breaking stress were similar to those found in the rats. There was in the rats an increase in Young's modulus of elasticity as the diet improved. The best way to compare the three lots of bones is by stress-strain diagrams which, since the influence of the size of the bone has been eliminated by calculation, allow direct comparison of the bony material in each group. The breaking stress and Young's modulus have been found to be very closely correlated, and since Young's modulus, unlike breaking stress, can be measured without damage to the bone, it may be that here we have a hint of a method which might be applied to living bone material. So far as we can tell at present the diminution in breaking stress and Young's modulus in rickets is due to the decrease in the amount of ash in the bones and is not associated with any chemical or structural alteration.

Normal bone is a remarkable material. The average breaking stress from our tests in bending is approximately 30,000 lb./sq.in. which is nearly as good as for cast iron. Young's modulus is, however, only one-tenth of that of cast iron. Thus bone, despite its lightness, is remarkably strong and its relatively great flexibility helps it to absorb sudden impacts.

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