THE ENDOCRINE BASIS FOR SLIPPING OF THE UPPER FEMORAL EPIPHYSES

An Experimental Study

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An endocrine basis for slipping of the upper femoral epiphysis is suggested by the fact that the lesion is nearly always accompanied by abnormalities of growth which in themselves appear to be caused by an endocrine disorder. This is especially true of those patients from whom an inadequate history of injury can be obtained. The usual disturbance of growth is the adiposo-genital syndrome, a condition characterised by obesity and deficient gonadal development; less commonly there is a history of very rapid growth, resulting in a tall, thin child (Key 1926). In the obese children there appears to be a low level of sex-hormone in the circulation; while in the tall, thin children there seems to be an excessively high level of growth-hormone. Both growth-hormone and sex-hormone alter the rate of proliferation of the cartilage cells in the epiphysial plates, with consequent changes in the thickness of the plates and in the rate of skeletal growth. Anterior pituitary growth-hormone stimulates the proliferation of these cells directly, with increase in the thickness of the plates and in the rate of skeletal growth (Ray et al. 1941). The sex-hormones slow the proliferation of these cells with decrease in the thickness of the plates and in the rate of skeletal growth (Gardner et al. 1943). Oestrogen produces this effect by inhibiting the secretion of growth-hormone by the anterior pituitary, rather than by direct action on the epiphysial plate (Zondek 1936). It is probable that testosterone acts in the same manner, although the evidence on this point is not as clear as in the case of oestrogen (Rubinstein et al. 1939).

From these observations it appears that between the time of activation of the gonads and the time that growth ceases, the structure of the epiphysial plates could be dependent on the relative levels of growth-hormone and sex-hormone in the circulation. Since it is during this interval that slipping of the upper femoral epiphysis occurs, with its associated abnormalities of growth, and since these growth disturbances are characterised by evident alterations in the level of growth-hormone and sex-hormone, it is not unreasonable to assume that an imbalance between these two endocrines is the cause of structural weakness in the epiphysial plates which makes them more susceptible to shearing stress. To test this hypothesis, an apparatus was used to measure the shearing strength of the epiphysial plates of rats. This paper reports observations made with this apparatus on animals receiving growth-hormone, animals receiving oestrogen and untreated control animals.

MATERIALS AND METHODS

Young albino rats of the Wistar strain, weighing approximately 150 grams, were used throughout the experiment. These were separated into three groups, each comprising five male and five female animals. The animals of one group were untreated and used as controls; those of a second group were gonadectomised and given 1 milligram of anterior pituitary growth-hormone, intraperitoneally, daily†; those of the third group were given 200 gamma

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† The growth hormone was prepared according to the procedure described by White (1944). The animals were gonadectomised in order to eliminate the effect of possible contamination of the growth hormone preparation with gonadotrophic hormone.
Apparatus used for determining the shearing strength of epiphyseal plates. The clamp was cut from quarter-inch aluminium plate. Each arm was fitted with a phonograph needle (one of them adjustable) which grasped the epiphysis securely. Crushing of the shaft of the bone was prevented by inserting it through a one-holed rubber stopper which was in turn clamped between the jaws of the vice.

of oestradiol benzoate in oil, intramuscularly, three times weekly. The animals were fed on a diet of Purina Fox Chow to which sufficient amounts of vitamins A and D were added; they were maintained in separate cages according to their group and sex.

After twenty-eight days, the animals were killed by chloroform and both tibiae were dissected out. One tibia was freed of muscle and soft tissue, and fastened by its shaft in the apparatus illustrated in Fig. 1, with its anterior border facing downwards (to eliminate the interfering effect of the projection of the tibial tuberosity on the shearing strength of the plate) and with its proximal epiphysis projecting from the vice. The clamp (Fig. 1, inset), with the empty bucket suspended from it, was fastened to the proximal epiphysis, and sand was poured into the bucket until the epiphysis separated. The weight of the bucket and its contents was recorded and used as a measure of the shearing force required to detach the epiphysis. The other tibia was fixed and decalcified in Bouin’s fluid and sectioned longitudinally by the paraffin method.

In addition to this material, tibiae from several normal rats, also weighing about 150 grams, were obtained. Some were sectioned without decalcification and stained for calcium distribution by the von Kossa method. Others were stripped of soft tissue, and
the proximal epiphysis was partly detached from the shaft, after which the specimens were stained for phosphate distribution by the Gömöri technique (Gömöri 1933).

**RESULTS**

The force required to detach the epiphyses in each group of animals is summarised by the graph in Figure 2, and shown in detail in Table 1.

**Histological changes**—1) *Growth-hormone treated animals*—On superficial examination, the epiphysial plates of the animals in this group appeared to be normal. However, on comparing them with the controls they were found to be much thicker than in the normal rats (Figs. 4a and 4b). This thickening occurred chiefly in the layers of proliferating and maturing cartilage cells in the plate. In addition, numerous mitotic figures were found amongst the cells on the epiphysial side of the plate (Fig. 5). These were seldom found in the epiphysial plates of normal animals.
2) Oestrogen treated animals—The epiphysial plates from these animals (Fig. 4c) were much thinner than those from the control group (Fig. 4b). The cells in the cartilaginous part of the plates were irregularly arranged and did not form orderly rows as in the normal animals. In addition, the trabeculae in the metaphysis were increased in number and thickness. This increased bone formation invaded the layer of hypertrophied cartilage cells on the diaphysial side of the plate (Fig. 6).

DISCUSSION

The structures in the normal epiphysial plate that are responsible for its strength can be identified in longitudinal sections. When seen in this manner, the plate may be divided into four layers (Fig. 7). 1) A layer of resting cartilage cells on the epiphysial side of the plate. These cells are arranged in irregular clusters, separated from one another by abundant cartilage intercellular substance which is in firm contact with the cortical bone of the epiphysis. 2) The next layer consists of proliferating cartilage cells arranged in orderly rows parallel to the long axis of the bone. Each row is separated from its fellows by intercellular substance containing bundles of collagenic fibrils (Fig. 3). These fibrils make a significant contribution to the strength of the plate in this region. 3) As new cartilage is added to the advancing edge of the plate by the division of cartilage in the second layer, those cartilage cells already present enlarge as they grow older, forming a layer of hypertrophied cartilage cells. The lacunae of these cells become so large that the intercellular substance remaining between them forms thin, delicate walls upon which the third layer is entirely dependent for its strength. 4) The diaphysial side of the layer of hypertrophied cartilage cells is strengthened, however, by the precipitation of mineral salts in its intercellular substance (Fig. 8). This forms the fourth layer of the plate, and is commonly termed the "zone of provisional calcification." In addition to these four layers, the region of trabecular formation in the metaphysis also contributes to the strength of the plate. Here osteoblasts lay down bone matrix about the spurs of calcified intercellular substance on the diaphysial side of the fourth layer, thus uniting the plate firmly to the shaft of the bone and materially increasing its strength.

It may be expected from this description that the weakest part of the plate is its third layer, where its strength is entirely dependent on thin, delicate walls of uncalcified intercellular substance. That this is true was first demonstrated by Haas (1917) who found that, when the periosteum about the periphery of an epiphysial plate was removed, the epiphysis could be detached from the shaft by gentle pressure. The line of separation was constant, always passing through the layer of hypertrophied cartilage cells. The demonstration of Haas is made more striking by staining the material for mineral distribution when it may be seen clearly that the plane of cleavage passes through the third layer (Fig. 9).
Proximal tibial epiphysial plate from each group of animals (× 150): (a) growth-hormone treated; (b) untreated control; (c) oestrogen treated.

Figure 4 shows the proximal tibial epiphysial plate from growth-hormone treated animal (× 400). Note mitotic figures in second layer.

Figure 5 shows the proximal tibial epiphysial plate from oestrogen treated animal (× 350). Note decrease in thickness of the epiphysial plate; increased bone formation in the trabeculae, and the manner in which this has invaded the diaphysial side of the fourth layer of the plate.

Figure 7 shows the proximal tibial epiphysial plate, untreated control rat (× 300): (a) layer of resting cartilage cells; (b) layer of proliferating cartilage cells; (c) layer of hypertrophied cartilage cells; (d) zone of provisional calcification; (e) trabeculae formation in the metaplates.

Figure 8 shows the proximal tibial epiphysial plate, untreated rat, v. Kossa silver nitrate stain for calcium (× 200). Note that the zone of provisional calcification is confined to the diaphysial side of the layer of hypertrophied cells.
With establishment of the fact that the weakest part of the epiphysial plate is its third layer, the interpretation of the effects of growth-hormone and oestrogen on its shearing strength is facilitated, for the thickness of this layer is altered by each hormone. Growth-hormone increases the thickness of the third layer by increasing the rate of proliferation of the cartilage cells in the second layer, thus making more cartilage cells available for maturation. The consequent increase in thickness of the third layer makes the plates more susceptible to shearing stress and therefore less force is required to detach the epiphyses in the animals given growth-hormone.

By interfering with the secretion of growth-hormone from the anterior pituitary gland, oestrogen decreases the rate of proliferation of cartilage cells in the second layer of the plate. Fewer cartilage cells are therefore available for maturation, and the third layer decreases in thickness. In consequence, more force is required to detach the epiphyses in the animals given oestrogen. In addition to this indirect effect on the epiphysial plate, oestrogen apparently stimulates enchondral bone formation directly. In birds, this is related to the need for rapid mobilisation and storage of calcium during the ovulatory cycle (Bloom et al. 1940), but in mammals the nature of the phenomenon is not clearly established. In any case, it contributes further to the narrowing of the third layer and hence to the strength of the plate.

The histological changes produced in the epiphysial plates by growth-hormone and oestrogen have been described by previous investigators. This paper relates these structural changes to alterations in the shearing strength of the epiphysial plate: growth-hormone decreases the shearing strength of the plate while oestrogen increases it. Since oestrogen exerts its effect primarily by inhibiting the secretion of growth-hormone by the anterior pituitary gland rather than by a direct action on the epiphysial plate, it seems that the strength of the plate is dependent ultimately on the balance, or ratio, achieved between the concentrations of these two hormones in the circulation. When this ratio is disturbed in favour of growth-hormone, the epiphysial plates undergo a decrease in shearing strength.

The abnormalities of growth associated with slipping of the upper femoral epiphysis in man suggest that the growth-hormone: sex-hormone ratio has been disturbed in favour of growth-hormone. This could occur in either of two ways: 1) by decreased sex-hormone secretion such as occurs in the adiposo-genital syndrome; or 2) by increased growth-hormone secretion such as occurs in the tall, thin, rapidly growing child. In each case, the actual quantity of each hormone secreted is of relatively little consequence, but the ratio between the two is the all-important factor affecting the shearing strength of the epiphysial plates. Thus, although the amount of growth-hormone secreted in the adiposo-genital syndrome may be less than usual, it is still far in excess of the sex-hormone; and although the amount of sex-hormone secreted in the tall, thin, rapidly growing child may be sufficient to produce secondary sex changes, it is still insufficient to control the already enormous secretion of growth-hormone. In both these disturbances of growth the end-result
is the same: the epiphysial plates come under the predominant influence of growth-hormone and, therefore, undergo a decrease in shearing strength just as occurred in experimental animals. It is probable that every epiphysial plate in the body is similarly affected by this process. But the upper femoral epiphysial plate is alone subjected to shearing during normal weight-bearing and may give way, perhaps after trivial injury which passes unnoticed in the hurly-burly of everyday adolescent life.

Oestrogen was selected for the experiments reported in this paper because it is well known that it produces typical histological changes even when given in relatively small amounts. The action of testosterone is less clear-cut: when given in small amounts it stimulates growth; but when given in large amounts it inhibits growth (Rubinstein et al. 1939, 1940). Preliminary experiments on the effect of testosterone on the shearing strength of the epiphysial plates confirm these findings. Testosterone must be given in large amounts, and over a fairly long period of time, before it increases the shearing strength of the epiphysial plates. The proximal tibial epiphysis was chosen because it is the largest in the rat, and because with the exception of the projection for the tibial tuberosity, its epiphysial plate has no irregularities which might interfere with the calculation of its shearing strength.

Summary and Conclusions—1. An apparatus was designed to determine the shearing strength of the upper tibial epiphysis in the rat. Observations were made with this instrument on normal animals, on animals receiving growth-hormone, and on animals receiving oestrogen. 2. When the epiphysis separates from the diaphysis, the plane of cleavage is constant, passing through the third layer of the epiphysial plate. 3. Growth-hormone decreases and sex-hormone increases the shearing strength of the epiphysial plate. These changes are due to alterations produced by these two hormones in the thickness of the third layer of the epiphysial plate. 4. It is suggested that these findings may be of significance in providing an anatomical basis for slipping of the upper femoral epiphysis in man, especially when it is associated with the adiposo-genital syndrome or with rapid adolescent growth.

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REFERENCES


