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EXPERIMENTAL INVESTIGATIONS INTO THE AETIOLOGY OF CALVE-PERTHES' DISEASE

BY

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Through the years there appear regularly new theories about the aetiology of Calvé-Perthes' disease. In them can be detected a well-founded doubt about *Axhausen*'s theory, which has otherwise been widely accepted.

Gradually all possible causes have been considered in the search for an explanation of *Calvé-Perthes'* disease and related conditions. The following review does not claim to be complete; it aims only to give an impression of the multiplicity of theories.

It has often been suggested that the basis of the condition must be either hereditary or constitutional. This idea is supported by the observations of *Aage Nielsen* and *Moltzen-Nielsen.*

Ribbing based his theory on the assumption of small abnormal bone nuclei having fragile and vulnerable connection with the surrounding tissue.

Göcke sought a purely physical explanation, assuming that the elasticity and resistance of the cancellous bone was reduced by small traumata.

Block gave a chemical explanation: a disturbance of water and salt metabolism.

The frequent occurrence of the condition in individuals of so-called "endocrine" character draws attention to the possibility of a hormonal disturbance.

Fromme considers that the condition resembles rickets.

Infection (e.g. syphilis) and toxic poisoning were early rejected as causes, since they were not supported by the histological findings.

The possibility of tumor formation—chondroma or giant cell tumor—has been considered (*Preiser* and *Fraenkel*).

Amongst investigators in recent years *Nagura* has been the most energetic champion of trauma as the main cause of the condition. He thought he found, in a specimen of osteochondritis of the elbow, slight solution of continuity with a resulting "demarcation process of the cartilage". Using young rabbits he submitted the femoral head to small traumata and produced mixed states of ossification which he compared with *Calvé-Perthes'* disease. He described these process in the following way:

1) First breakdown: the small primary lesion.
2) First repair: the formation of cartilage callus and ossification.
3) Second breakdown, which occurs when satisfactory conditions for regeneration are lacking; it consists of regressive changes determined by the mechanical factors.
4) Second repair.

Calvé-Perthes' disease should be the same as the second breakdown and the second repair. *Nagura* does not explain the predilection for a certain age and site, the familial incidence, etc.

Impaired and increased blood-supply have also been considered. *Legg,* who was one of the first to study the disease, in 1908, thought that the vessels at the junction between the femoral neck and epiphysis might be interrupted by injury.

Axhausen thought that the condition was based on a necrosis due to obstruction of the arteries with emboli, which were probably non-infective bacterial emboli. The theory was based on observations of necrosis of the whole or parts of the epiphysis. Certainly necrosis can be found. But if the histological studies of *Calvé-Perthes'* disease are examined one

finds that necrosis is by no means a predominating or constant characteristic; cases have even been described where there was no necrosis (*Motojima*). This theory fails to explain the most typical characters: familial incidence, preference for one sex, simultaneous appearance of changes in the head and acetabulum, etc.

Ipsen introduced arterial spasm into the discussion.

Leriche thinks that hyperaemia may explain the condition.

Bentzon recognised that it was a proliferative process—a kind of "pathological callus formation"—and this seems to me to be of great importance for the further study of the disease. The theory is that the process develops from a hyperaemia due to minor lesions of the very vulnerable nerve elements which play a part in the vasomotor regulation. Certainly, however, there must be local and general changes to start the process. *Bentzon* thought that he would find support for his views by experiments in which alcohol was injected round the vessels and nerves concerned, using young rabbits.

The theories already mentioned have hardly passed the stage of stating the problem and I have therefore tried by basing my investigations on *Bentzon*'s work, to carry further those studies which seemed to me to have most nearly reproduced *Calvé-Perthes'* disease.

In the first series of experiments 28 rabbits aged between 4 and 7 weeks were used. 0.25 ml. 80 % sterile alcohol was injected on the inferior side of the R. femoral neck at the place where the main artery to the head is usually found. The aim was to submit the vessels, and the nerves, to a 'traumatic' effect. Marked changes were found in 2 animals aged 4 weeks and slight changes in 4 between 4 and 5 weeks. Radiography showed slight flattening of the head, often with increased growth on the medial side of the neck, and valgus

position. The surface of the head showed slight condensation and waviness. In 2 animals there were definite microscopic changes similar to those found in the second series.

In the second series of experiments alcohol was injected into 26 young rabbits as in the first series, but the injections

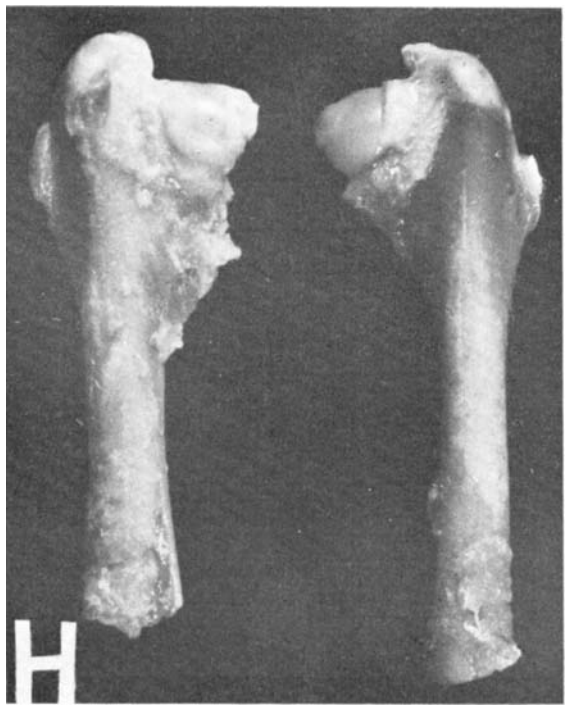

Fig. 1.

were repeated 2 to 4 times at intervals of a few days. Here also a marked difference was found between the different age-groups: all except one of the 4-week-old rabbits showed marked changes, while the slightly older animals, 6-10 weeks, showed only slight changes, and 6 showed no changes at all.

Macroscopically there was flattening of the femoral head corresponding to the uppermost weightbearing part. The cartilaginous surface was irregularly waved with depressions

in it. The cartilage was yellowish, and seemed to be less transparent than on the sound side (fig. 1).

Radiography showed the following changes (fig. 2): flattening of the head with an irregular joint surface, often wavy, but sometimes roughened. The head itself was usually condensed, especially in the subchondral zone. In some pic-

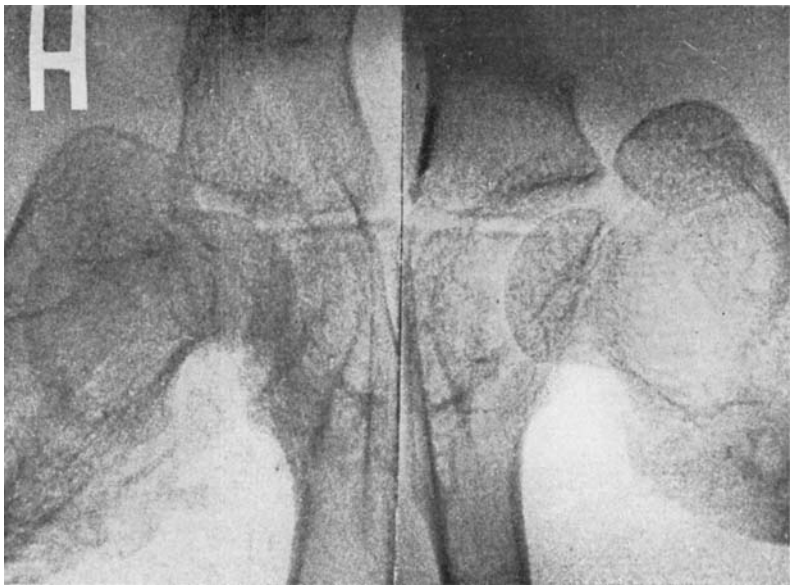

Fig. 2.

tures there were small transparencies. The epiphyseal cartilage showed very marked changes: it was increased in breadth with a more irregular wavy formation and indefinite outlines. Usually the neck showed rather diffuse, rarely patchy, transparency. In many of the cases a valgus deformity of the neck had developed. On the inferior surface of the neck there was usually a reaction to the alcohol injection: sometimes flat, and sometimes bulbous proliferations or spur-shaped formations.

Microscopy showed marked changes in 20 animals: again the head showed an irregular and flattened outline. The joint

cartilage was wavy with some thick and some thin parts. In some cases the cartilage cells were in small areas numerous but irregularly arranged. The trabeculae showed marked variations in their arrangement; usually they were strikingly widely spaced with irregularly-shaped meshes; in other cases there was in small parts a closer, but still irregular arrange-

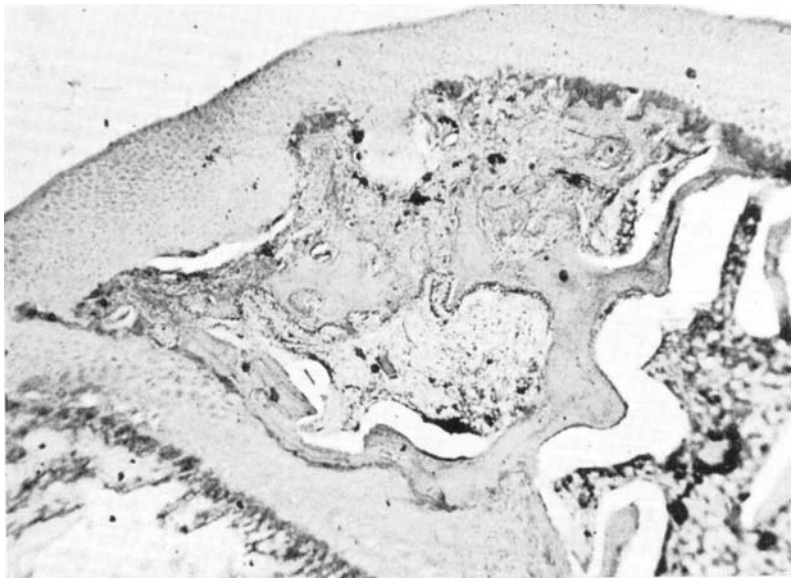

Fig. 3.

ment of the trabeculae, though there was still wide variation; some were rather thin, and seemed more primitive, others were thick. In these parts there was considerable osteoblast activity (fig. 3). An almost constant change was an irregular widening of the epiphyseal cartilage. Many times small mushroom-shaped outgrowths consisting of cartilage cells were found (fig. 4). In one preparation the medial part of the epiphyseal cartilage was penetrated by a cellular connective tissue, which seemed to be preparing the way for a callus-like tissue. In some preparations there were changes in the epiphyseal cartilage which must be considered as necroses: poor

and no staining of the nuclei. Similar changes were seen in the joint cartilage and in sections of the bony part of the head, where some cases showed definite necrosis (fig. 5). In one place an ingrowth from the marrow into the necrotic part was seen. The marrow was usually fibrosed. In cases which had been allowed to live several weeks after the in-

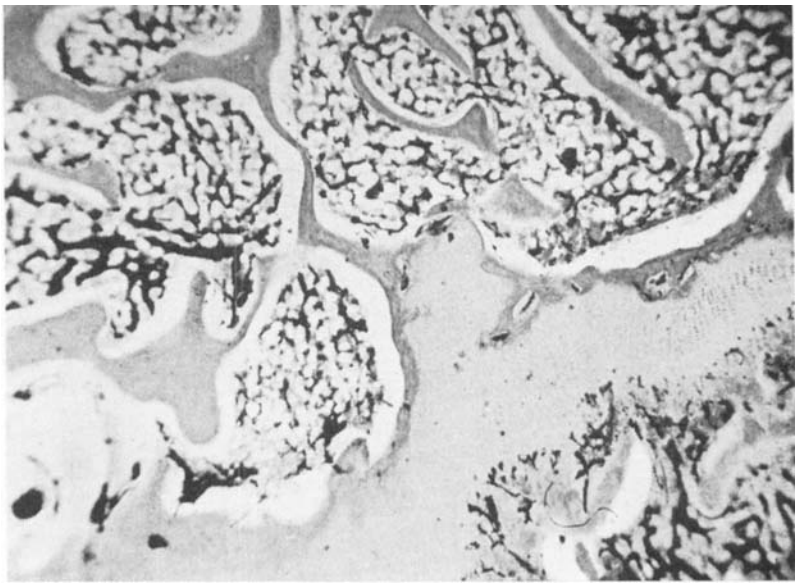

Fig. 4.

jections the marrow seemed to have been converted into fatty marrow, and, similarly, the other changes showed a tendency to return to normal. At the site of the injections there were marked changes most often consisting of tumor-like masses of a primitive tissue resembling cartilage.

Various injection and staining methods were attempted to demonstrate the condition of the circulation. Injection of red-lead-gelatine showed the course of the arteries, and confirmed that the main artery ran under the neck; other methods were also used. Indian ink-gelatine gave good pictures of the arrangement of the vessels. No new formation of vessels was

seen in the head, but there was rich proliferation of vessels round the site of the alcohol injections. When the vessels were artificially distended by the injection these methods gave no true impression of the degree of filling of the blood vessels. There were some technical difficulties in demonstrating the degree of filling, but staining the red blood corpuscles was

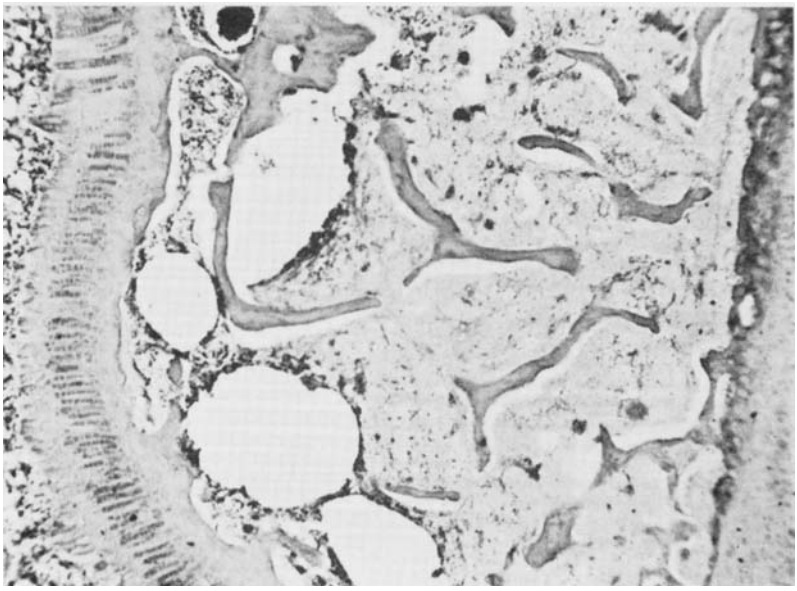

Fig. 5.

fairly successful (using a modification of Weigert's stain). No definite hyperaemia could be found in the treated hips.

In the 3rd series an attempt was made to produce an artificial hyperaemia by daily injections of procaine. No changes could be detected. The blood-filling was the same on the treated and untreated sides.

In the 4th series, 11 rabbits were used, and small fissures were made percutaneously in the femoral neck to study the importance of direct trauma. No changes were seen in the head.

In the 5th series Varex was injected round the vessels of

the femoral neck in a few animals, in the hope that the blood-supply might be interrupted. Again there were no results, and especially there were no areas of necrosis.

Thus changes were produced in the femoral head, and were more marked the younger was the animal and the greater the irritation. The changes consisted of those which are seen in the breakdown and repair of bone and which lead to changes in the shape and structure of the capital epiphysis.

It is not clear what kind of action is produced by the injection of alcohol round the neurovascular bundles. It does not seem that a significant hyperaemia occurs. But by analogy with experiences elsewhere one must assume that the alcohol interrupts the nerves and thus acts on the capital epiphysis. One cannot speak of a direct action, since it was injected at some distance from the head.

Are the changes which were produced identical with those of Calvé-Perthes' disease? One certainly cannot prove it, but it seems to me that there are so many features common to both that it is justifiable to base some ideas about the character and aetiology of the disease on the results: in animals, during growth, there have been seen macroscopical and radiographical changes, necroses, cartilage formation and regeneration processes, that is to say the same components which form the mixed histological pictures of Calvé-Perthes' disease, which we know from some, though only few, investigations. One cannot expect to produce an exactly similar disease picture in experimental animals in whom weightbearing is different and the disorder does not occur spontaneously.

As a result of my experiments I have come to the conclusion that the disorder consists of a disturbance of the natural growth of the bone, in which there is an interference with the factors that determine the normal differentiation of the cells and the structure and shape of the tissue.

About the differentiation of bone tissue we know so far, from work by *Fischer* and *Parker,* and *Fell,* and others, that it originates from a fibroblast-like cell without any special characteristics. However, this cell has the property, when the

conditions are suitable, of forming the starting-point for the cartilaginous skeleton and can further develop into bone cells. In in-vitro studies in which the primitive mesenchymal cell has been isolated from the parent organism it has been possible to make it differentiate so that a tissue is produced which is by no means unlike the corresponding supporting tissue in the parent organism. It seems, therefore, as if the primitive cell has the property of very advanced differentiation though not sufficient to form the different organs, and so to reproduce the organism. One cannot avoid the view that there must be a common regulating factor (which is not simply the same as the presumed growth hormone) which determines the development of the organs in an individual.

I suggest that it is at this point that in Calvé-Perthes' and similar diseases disturbance occurs and the controlling co-ordinating factor disappears. The bony tissue is then forced to take on a more primitive form of growth: cartilage is formed in preference to bone and the bone elements are found and arranged at random. Since this tissue is presumably less suited to weight bearing the affected parts of the bone are deformed according to the strains and trauma to which they are submitted.

Both clinical and experimental observations suggest that the process is not started by a single factor, but by a series of contibutory causes. One may imagine that the regulation of growth is lost when the sum of these causes exceeds a certain limit.

Amongst them there is without doubt a constitutional, probably hereditary, factor. It is not possible to say what constitutes this factor, but it may be a matter of anatomical variations, e.g. in the course of the vessels and nerves, or a reduction in the stability with which the organism finds its shape. Thus the hip-joint is certainly a "locus minor resistentiae" in the locomotor system. The frequent occurrence of variations and the large number of arthroses suggest that there is a certain "incompleteness" of the hip-joint, a certain failure to stand up to the strain which is laid on it; from this

it is not far to the view that the "growth stability" of the joint is relatively small and can easily be upset.

Next we must point to the hormonal regulation. Here our knowledge is still very limited. We know the hormones which control the main tendencies of growth; we must find those which regulate the growth of different organs.

One must also consider the age. One can imagine that, at the time when the condition appears, there is a labile balance between the components of the joint—cartilage and bone—which can be upset by external factors.

Finally clinical experience suggests that trauma can play a part in the aetiology. This view is supported by the results of the experiments. But in the word 'trauma' I include all external factors of more than 'physiological' intensity, which cause a disturbance of the organism's normal function. Especially may one include small mechanical influences which under normal conditions will hardly have any harmful influence, but which, in special conditions, e.g. anatomical variations, can act on the mentioned growth-regulating factors so that the normal rhythm is disturbed. How far the point of attack is the nerves, how far the vessels, or perhaps quite other structures must be left undecided.

Thus it has not been possible to obtain an explanation of Calvé-Perthe's disease based on facts. Since I have included various unknown conditions in my discussion it cannot be considered as more than a hypothesis. However I hope that my experiments and ideas may form the basis for a more fruitful work on these problems. We can expect to get the final answer when the study of cells has elucidated growth and the determination of form; it will then be possible to test the views expressed here by more exact methods.

SUMMARY

By injecting alcohol round the vessels and nerves running to the femoral head in young rabbits macroscopic, radio-

graphic and histological changes similar to those of Calvé-Perthe's disease were produced.

From these findings it is suggested that Calvé-Perthe's disease is produced by a disturbance of the natural growth of bone tissue due to an action on the factors which determine the differentiation of the cells and the structure and shape of the tissue so that a more primitive form of growth predominates. The process is thought to be initiated by a number of causes, amongst which the constitutional, hormonal and traumatic are emphasised here.

RESUME

Au cours d'expériences pratiquées chez de jeunes lapins auxquels on a injecté de l'alcool dans les vaisseaux et les nerfs entourant la tête fémorale, on a réussi à provoquer des modifications qui tant au point de vue macroscopique, radiologique qu'histologique montrent beaucoup de ressemblance avec la maladie Calvé-Perthes.

Sur la base de ces recherches, il est allégué que la maladie Calvé-Perthés est due à une perturbation de la croissance normale du tissu osseux, à savoir une perturbartion des facteurs qui conditionnent la différenciation des cellules, ainsi que la structure et la forme des tissus, les formes de croissance plus primitives devenant prédominantes. Toute une série de causes semblent pouvoir déclencher ces processus parmi lesquels on relève des facteurs d'ordre constitutionnel, hormonal et traumatique.

ZUSAMMENFASSUNG

Bei Versuchen, in denen jungen Kaninchen Alkohol um die zum Caput femoris laufenden Gefässe und Nerven injiziert wurde, wurden Veränderungen erzeugt, die macroskopisch, röntgenologisch und histologisch eine grosse Aehnlichkeit mit Mb. Calvé-Perthes zeigten.

Auf Grund dieser Versuche wird die Vermutung ausgesprochen, dass der Mb. Calvé-Perthes auf einer Störung des

natürlichen Wachstums des Knochengewebes beruht, in der Weise, dass die Faktoren, welche die Differenzierung der Zellen und die Struktur und Form des Gewebes bestimmen, beeinflusst werden, so dass primitivere Wachstumsformen dominieren. Man denkt sich, dass der Prozess aus verschiedenen Ursachen in Gang kommen kann, unter denen konstitutionelle, hormonale und traumatische Faktoren hervorgehoben werden.

DISCUSSION

Bentzon, Thomasen, Morville, Stören, Sodeman, Randløv-Madsen.