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Philip H. McFarland

Harold M. Frost

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A POSSIBLE NEW CAUSE FOR ASEPtic NECROSIS OF THE FEMORAL HEAD

PHILIP H. McFARLAND, M.D. AND HAROLD M. FROST, M.D.

INTRODUCTION

Aseptic necrosis was first described pathologically by König in 1888 when he labelled osteochondritis dissecans a "quiet necrosis". Since that time we have learned that the blood supply to bone may be interrupted by several known means. These means include physical interruption by fracture, arterial and arteriolar embolism, venous and arterial thrombosis, Caisson's disease, Gaucher's disease, sickle cell anemia, hemophilia and others, including the inevitable idiopathic.\(^1\)\(^,\)\(^12\) We would like to direct attention to the atraumatic causes and present a possible new cause of aseptic necrosis of the femoral head in the human adult.

The currently accepted version of the pathological events that occur in aseptic necrosis of bone divides the phenomena into 3 phases.\(^1\)\(^,\)\(^12\)

1) **Onset of cellular necrosis.** This follows interruption of the blood supply, and may be massive or focal, depending on the nature of the vascular disturbance. Death of the cells is followed by autolysis which is apparent microscopically but is not apparent by x-ray. Some time after the necrosis, osteoporosis of the surrounding, healthy bone may begin to develop which leads to a relative increase in radiodensity of the affected bone but not necessarily an absolute increase.

2) **Removal of dead bone.** This stage begins to develop within about a week of the onset of the necrosis and consists of the proliferation of granulation tissue arising from the healthy bone adjoining the dead bone. The granulation tissue absorbs the dead bone with the aid of osteoclasts. This resorptive activity is usually focal, leading to an x-ray appearance in this phase of mottled radiolucencies in the dead bone.

3) **Reossification.** In this phase, regeneration occurs, the areas where dead bone had been absorbed now being filled with new bone, while in other areas new bone is deposited on the surfaces of dead bone trabeculae. Often in this phase there is also some gross crumbling of the affected bone, which in effect, but not in actuality, has been grossly softened by the preceding events. Marked mottling and irregularity appears on the x-ray during this phase because of the osteoporosis of the surrounding live bone, crumbling with trabecular impaction and overlap in the dead bone, focal areas of destruction of old bone, and deposition of new bone on the trabeculae of dead, unabsorbed bone.

In any given case of avascular necrosis of bone, one will probably find all three phases going on simultaneously in different parts of the affected bone, and this contributes materially to the apparent irregularity of the process and the initial appearance of lack of order in microscopic sections.

The authors wish to thank Dr. Richmond Smith, of the Department of Endocrinology, and Dr. J. L. Fleming, of the Department of Orthopedic Surgery, for their contribution of the cases, and for their cogent advice and thinking in the preparation of this paper. The paper was originally prepared for and read before the Detroit Academy of Orthopaedic Surgery in May, 1959, by Dr. McFarland, and with the assistance in preparation of Drs. Smith and Fleming, and is presented here with some modification necessitated by difference in audience and purpose.
We will see a bit later that in some instances this picture of the events is probably too clear and in actuality the events are more complex.

**Hypercortisonism:** We would like to postulate hypercortisonism as an additional cause of avascular necrosis of the femoral head. It is well known that the pathological changes characteristic of Cushing's disease are simulated by the administration of large amounts of exogenous cortisone. It has come to be accepted that the features of Cushing's disease and of exogenous hypercortisonism are identical. It is known that endogenous and exogenous cortisone have an unfavorable effect on protein metabolism, increasing protein catabolic activity.

It will be recalled that Cushing's disease and Cushing's syndrome are characterized by glycosuria, moon face, buffalo hump, truncal obesity, osteoporosis, thin, reddish skin which bruises easily and contains purplish striae, hypertension, muscular wasting and protruberant abdomen. It is felt that the easy bruising is due to atrophy of the walls of blood vessels.

In recent years we have seen two adults at Henry Ford Hospital who had hypercortisonism and also had avascular necrosis of the femoral head. In one case the source of cortisone was endogenous, in the other exogenous.

**CASE PRESENTATION**

1) The first case is a 49 year old Caucasian woman who presented with a history of 4 years of increasing pain and stiffness in one hip without any history of trauma. X-rays taken a year before her first Henry Ford Hospital visit revealed an early aseptic necrosis of the right hip.

The woman had the stigmata of Cushing's syndrome by history, by physical examination and on extensive laboratory tests. The cause of the condition was obscure. Although she had been taking cortisone exogenously prior to her first Henry Ford Hospital visit, this was far too short a time to explain her Cushing's picture, the doses were too small, and the x-ray taken a year before her appearance at Henry Ford Hospital antedated the administration of cortisone by more than 9 months. This patient subsequently had a bilateral adrenalectomy. No tumor was found in the adrenals and the patient has been lost to follow-up. The patient's x-rays revealed, in addition to the hip lesion, an osteoporosis.

2) The second case is a 51 year old Caucasian man who developed rheumatoid arthritis 5 years prior to his first Henry Ford Hospital visit, had normal hips by x-ray a year prior to his visit but did reveal osteoporosis on these films, and had been on exogenous cortisone for some time prior to taking these films. When first seen at Henry Ford Hospital in 1957 an early aseptic necrosis of one hip was apparent on new x-rays. A femoral head endoprosthesis was put in this hip the same year, and another one put in the other hip a year later at the insistence of the patient, since that one had become painful in the interim.

When first seen at Henry Ford Hospital the patient had been on cortisone for more than 2 years, had his own source of supply of the drug which he would not
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Figure 1
AP x-ray view of both hips in the 2nd case described in the text. The hips reveal changes characteristic of so-called aseptic necrosis, the condition being worse in the hip on the left. Osteoporosis is also apparent.

Figure 2
The hips in the case in figure one after bilateral endoprostheses had been installed by Dr. Fleming.
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reveal or discontinue using, and was taking an average of 10 grains of codeine a day. He had the typical moon face, thin skin, purplish striae and multiple ecchymoses when first seen. He would be considered a somewhat uncooperative patient. (See Fig. 1,2,3).

![Figure 3](image)

Lateral view of the thoracic spine in the case in figure 1, revealing osteoporosis and somewhat prominent end-plate density.

**DISCUSSION**

Unfortunately, it was not possible to study the femoral heads in adequate fashion, in the first case, because there was no hip surgery, and in the second case due to error. Consequently proof or disproof of the speculations which follow must await additional material.
Figure 4
Low power photomicrograph of cancellous bone in the femoral head of a patient with rheumatoid arthritis who had received corticoids for a long time. An intracapsular hip fracture led to prosthetic replacement and submission of the specimen for study. The patient had a rather severe osteoporosis. The crosslines identify the area examined under high power in the next figure. Section prepared by Frost’s methods.

We may begin with the observation that in two patients who had hypercortisonism aseptic necrosis of the femoral heads developed. In one of the cases the oversupply was of exogenous, in the other of endogenous origin. This correlation has been noted
by others in cases of exogenous hypercortisonism and the presumptive conclusion is that the hormone somehow is responsible for the aseptic necrosis.11

How?

We entertain two separate lines of thought.

A) The first line of thought is related to the ease of bruising in hypercortisonism. It is possible that the vascular fragility responsible for this may lead to a focal hemorrhage and avascular necrosis. The femoral head is a likely site for the initial development of such changes in view of the known predilection of the femoral head to develop aseptic necrosis in the presence of the other causative factors referred to at the beginning of this paper.

B) The second line of thought is new and based on work recently done in the Henry Ford Hospital Orthopaedic Research Laboratory.

First, note that the Laboratory has demonstrated the existence of microscopic cracks in vivo in bone.9 These cracks presumably arise through a process similar to that occurring in the failure of metals.24 A repair process has also been visualized, explaining why these cracks do not accumulate in the skeleton, at least under normal conditions. Some of these cracks have been found to be labelled with tetracyclines administered in vivo, removing the last shred of doubt as to their reality.

Second, many have postulated that cortisone and its related compounds should exhibit a depressing effect on osteoblastic activity in man.6,7,8 In the past two years the Laboratory has succeeded in measuring this effect in man on lamellar osteoblastic activity by methods described elsewhere. The depressing effect of full therapeutic doses of cortisone and related compounds on lamellar osteoblastic activity may be disconcertingly large. Lamellar osteoblastic activity is reduced from 0.1 to 0.0001 of normal.9

The continual production of microscopic cracks, their continual repair, and the depressing effect of cortisone on osteoblastic activity, may be put together to provide a neat explanation of aseptic necrosis of the femoral head in hypercortisonism. The explanation is so neat that we expect to find some gaps in it later, since biological answers are rarely simple and rarely complete.

The synthesis is simple: We postulate that microcracks are part of the damage normally occurring as the result of daily wear and tear. It is possible that other types of damage also occur which are not as evident as cracks in our undecalcified sections. We know that osteoblastic activity is the only repair process available to bone. It might be expected then that marked retardation of this repair process would lead to progressively larger and larger accumulations of microcracks, and perhaps other types of faults, which in turn lead to the gross crumbling and to the reaction of the adjoining, undamaged tissues which are evident on x-ray and in decalcified sections. This concept also explains the pathological rib and vertebral fractures often found in exogenous hypercortisonism. In figures 5 and 6 appear photomicrographs of actual

*It was also necessary to measure the normal osteoblastic activity in man to determine this effect.
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Figure 5

High power view of central field in figure 4. A small microcrack is identified by the India Ink lines. This crack lies in the interior of the trabeculum and does not reach the surface of the section or the trabeculae. Plane of focus is about 15 microns beneath the section surface.

microcracks found in the femoral head of a 63 year old woman on exogenous steroids for rheumatoid arthritis. The specimen was obtained at surgery for a prosthetic replacement through the courtesy of Dr. C. White, of the Department of Orthopaedic Surgery.

The nucleus of a new concept is contained in the above paragraph. The idea
is that there is normal skeletal wear, normal skeletal repair of that wear, and interference with either side of the equation may lead to gross pathology. In the present situation we postulate that repair is retarded while wear is not, the result being aseptic necrosis of the femoral head.

It must be noted that our wear-repair hypothesis does not require that the affected femoral head be dead. It may instead be quite alive, at least as far as is consistent with the age of the patient. This is consistent with the findings by Evans and by Frost that there may be disconcertingly little tissue death detectable on sections through a femoral head with aseptic necrosis. It may well be that the term “aseptic necrosis” is merely a convenient clinical description of a symptom-sign-X-ray complex which may have a number of different causes with distinct pathology and pathogenesis. The presence of microcracks and the marked retardation of lamellar bone repair processes which have been found and measured in the Laboratory have not been given consideration in the current theories of pathogenesis of aseptic necrosis because they were unknown when these theories were being formulated.

SUMMARY

Two cases of hypercortisonism accompanied by avascular necrosis of the femoral head are presented. In one case the hypercortisonism was due to endogenous, in the other to exogenous causes. A causal relationship of the hormone to the event is postulated (as it has been postulated by others). Two possible modes of genesis of the femoral head changes are considered, one vascular, the other due to an effect of wear and an effect of cortisone on osteoblastic activity.

REFERENCES