EPIDEMIOLOGICAL AND ETIOLOGICAL CONSIDERATIONS IN OSTEONECROSIS

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In this paper will be examined some of the clinical and epidemiological characteristics of aseptic bone necrosis as it affects the head of the femur in the general population. This population does not include those who are subjected to decompression. Also to be discussed is the occurrence of coagulation and hematologic abnormalities in these patients, with speculation on how they may be related to excessive alcohol consumption and other systemic disturbances. It should be emphasized that in most instances aseptic bone necrosis is a skeletal manifestation of a very serious and generalized metabolic disturbance.

To understand the problem more clearly, a group of 50 patients afflicted with femoral-head necrosis was studied at the University of Iowa between 1951 and 1968 (Boettcher *et al.*, Part I, 1970; Boettcher *et al.*, Part II, 1970). The results are shown in Table I.

The condition is clearly not a matter of degeneration due to age. There must be some underlying disturbance that leads to the development of these skeletal lesions in a group whose ages range from 24 to 65 years.

Prior to the time of diagnosis, most patients had had symptoms for an average of 18 months; in some, symptoms had persisted as long as 5 years. In many instances a variety of false diagnoses had been made before the correct one was arrived at. Seven hips were asymptomatic at the time of diagnosis, meaning that the lesion had not progressed to the point of femoral-head collapse. Most likely the patient who experiences acute pain has probably at that point suffered some collapse of the weight-bearing segment.

Of our patients, 36 were afflicted bilaterally. This very high incidence of bilaterality was revealed through regular follow-up examinations of the patients, at which time radiographs were taken of both hips. We can say that if a patient has aseptic bone necrosis involving the head of the femur, the chances are perhaps three in four that the other femoral head will be similarly affected. In all, 86 hips in 50 patients were diseased.

When these patients were recalled for follow-up examinations, 45 out of the 50 returned; the other 5 were dead. The average age of these patients at death was 52 years, attesting to the severe generalized metabolic disturbance involved in this patient population.

By analyzing the 50 patients' records, reevaluating their histories, and reexamining them and their laboratory data, we attempted to uncover a common link among the cases or a factor that might in some way have contributed to their aseptic bone necrosis. The following are other diseases and conditions that these patients shared in association with osteonecrosis, all of which

Table I. FEMORAL-HEAD NECROSIS IN 50 PATIENTS*

Average age	46 years (age span, 24 to 65 years)
Duration of symptoms	18 months (span, 1 to 60 months)
Asymptomatic	7 hips
Bilateral necrosis	36 patients
Unilateral necrosis	14 patients
Total number hips	86
Adequate follow-up (36 patients)	55 hips

*44 males, 6 females

have been reported in the literature:

Excessive alcohol consumption	37
Hepatic disease	21
Gout or hyperuricemia	16
Thrombocytopenia	15
Thrombocythemia	6
Steroid therapy	9
Hypercholesteremia	5
Hyperlipidemia	1
Discoid lupus erythematosus	1
Systemic lupus erythematosus	1
Fabry's disease	1
Reynaud's disease	1
Gaucher's disease	1

As noted, 37 patients had a history of excessive alcohol consumption. We were rather conservative in what we labeled excessive, defining it as being three or more drinks of hard liquor per day, regularly. However, the alcohol consumption of most of these patients was much higher. Many were binge drinkers, consuming as much as a fifth [one-fifth gallon] per day. Twenty-one patients had hepatic disease. Hepatomegaly was palpated in 13; abnormal BSP retentions were found in 12; liver biopsies on 2 patients revealed sclerosis.

We became aware of the fact that bleeding and coagulation disorders seemed to occur with unusual frequency among the 50 patients. On the basis of their histories and our clinical observations, 11 were thought to manifest such disorders, namely:

Clotting Defect	Occurrences
Epistaxis	2
Bruising	4
Abnormal bleeding	3
Petechiae or purpura	3
Thrombosis	1
Menorrhagia	1
Wound hematoma	3
Retinal hemorrhage	1

Of the two patients with epistaxis, one had drug-induced thrombocytopenia. At that time he had a platelet count of only 5000. The second patient also had thrombocytopenia as well as hyperlipidemia; his cholesterol level at that time was over 1000.

Of the four patients reporting repeated and easy bruisability, abnormal surgical bleeding in the form of diffuse, persistent capillary oozing occurred in three. One patient, suffering from persistent deep-vein phlebitis with thrombosis, had an interesting family history in that his father had died at a young age of mesenteric thrombosis. When the patient with menorrhagia had a hysterectomy, she required 10 units of blood for transfusion and was subsequently found to have idiopathic thrombocytopenia. Three patients with low platelet counts had wound hematomas. One man with hyperlipidemia and thrombocytopenia had retinal hemorrhages.

Because of these findings, we studied the platelet counts in our patients, most of them in retrospective investigations. The curve in Fig. 1 shows the normal distribution of platelet counts

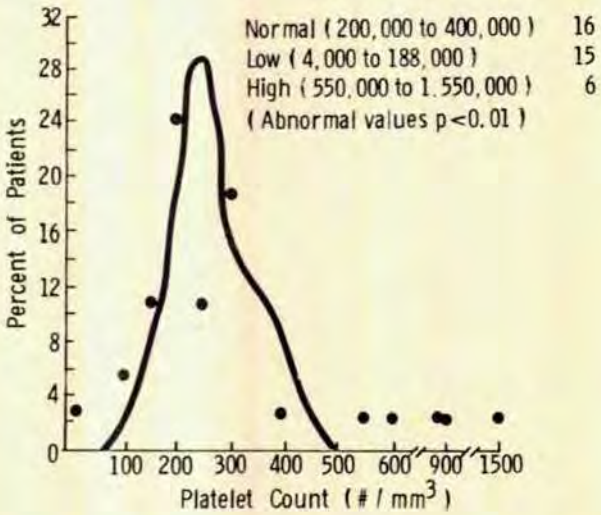

FIG. 1. Platelet counts in femoral-head necrosis in 37 patients, revealing abnormally high and low values in so-called idiopathic osteonecrosis. Normal range is within curve.

made in our laboratory on an unrelated group of patients as part of a different epidemiological study, the normal values being from 200,000 to 400,000. Of the 37 patients in our bone-necrosis investigation whose platelet counts were determined, 15 had low values and the platelets of 6 were elevated. The low values ranged down to 4000 — quite low. Some very elevated ones, as high as 1.5 million, were also recorded. The frequency of abnormal platelet counts, even in so small a subject population, is considered statistically significant.

We also studied the incidence of abnormal

serum uric acids in 33 patients; the normal value is 8 mg % or less. The graph in Fig. 2 shows a

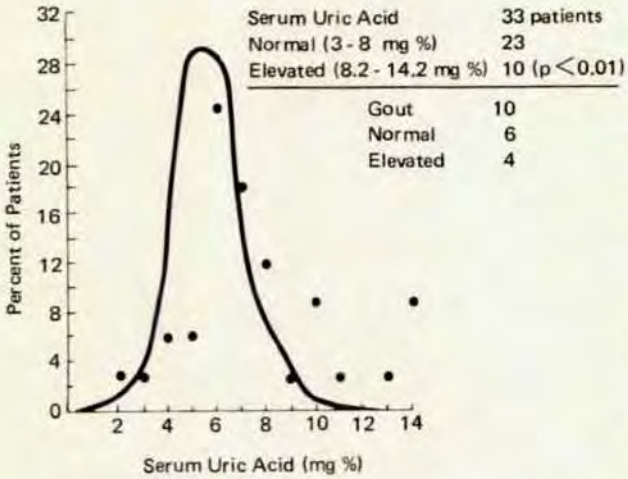

FIG. 2. Shift of abnormally high uric-acid values to right in 33 osteonecrosis patients in comparison with those of control group (under curve).

shift to the right. Serum uric-acid determinations of up to 14 mg % were recorded. Ten of these people were known to be under treatment for gout, which would have tended to reduce their uric acid to normal. So the value in an untreated population would probably have been even higher. The presence of abnormal levels of uric acid in this small a group of patients is also statistically significant.

After we became aware of the coagulation disorders in our patient population, we subjected 30 of them to the following rather extensive battery of coagulation tests:

Bleeding time

Clotting time

Silicone clotting time

Clot retraction

Prothrombin time (one stage)

Prothrombin time (two stage)

Thrombin time

Thromboplastin generation time

Prothrombin utilization (30 min)

Prothrombin utilization (60 min)

Plasma clotting time

Circulating anticoagulant

Fibrinogen

Factor VIII

Fibrinolysis plasma clot

The tests showed that at least one abnormal condition existed in every patient, which of itself is not significant. However, 9 patients revealed a combination of several coagulation abnormalities; the evidence suggested a hypercoagulable tendency in 5 of them and a hypocoagulable tendency in the other 4.

Coagulation and platelet-count abnormalities plus observations of bleeding and hemorrhages — together with an overlap among the disorders — appeared to offer some direct evidence for the existence of a bleeding or clotting disorder in 26 of the 50 patients:

Findings	Number of patients
Abnormal coagulation battery	9
Abnormal platelets	21
History or clinical observations of abnormality	11

There was some alteration in hemostasis as well. Considering the high incidence of alcoholism and other disorders, we then speculated about the possible existence of other bleeding and clotting abnormalities which we were unable to measure at that particular time. With excessive alcohol consumption in humans, intravascular red-cell agglutination is known to occur. Sludging and stasis have been observed in the small vessels of the eye, as have microhemorrhages. It is interesting that with excessive ingestion a marked thrombocytopenia occurs within a few hours, followed by rebound thrombocytosis when alcohol is withdrawn. When significant amounts of alcohol are consumed, especially in binge drinking, platelet counts will fluctuate markedly. An increase in fibrinolytic activity is also well known, especially (for some reason) following ingestion of beer.

Many coagulation factors are produced in the liver. Likewise, many coagulation abnormalities are associated with liver disease. For example:

Prothrombin deficiency	Factor X deficiency
Factor V deficiency	Factor XI deficiency
Factor VII deficiency	Thrombocytopenia
Factor IX deficiency	Increased fibrinolytic activity

As stated, 21 of our 50 patients had serious liver disease. Not all were sclerotic or had a large fatty liver, but they suffered from deficiency states of prothrombin. Several of the clotting factors, as well as thrombocytopenia and increased fibrinolytic activity, can occur with liver disease.

With hyperuricemia, increased platelet adhesiveness is common. Increased platelet turnover, increased plasma thromboplastin activity, and activation of the Hageman or clotting factor may also occur. Alcohol consumption compounds the problem, as it tends to raise the blood uric-acid level as well.

Several of our patients had hyperlipidemia, which is associated with such bleeding and clotting problems as marked acceleration of thrombus formation, decreased clotting time, modification of the thromboplastin generation time, and increased fibrinogen and clot retraction.

Nine patients in this study had undergone steroid therapy. This suggested to us that the underlying disorder for which steroids were given might have been of equal or even greater importance to the etiology of bone necrosis than the steroids themselves. Steroids, as one knows, may be prescribed for everything from the common cold to gout. In our patient population they had been administered for the following disorders:

Disorder	Number of patients
Thrombocytopenia	2
Thrombocythemia	1
Polycythemia	1
Systemic lupus erythematosus	1
Discoid lupus erythematosus	1
Gout	3

The two patients receiving steroids for thrombocytopenia had done so on a relatively long-term basis. Was the thrombocytopenia (in one case with 5000 platelets) more a contributory factor in the bone necrosis than the steroids were? It might be mentioned that aseptic bone necrosis has been reported in systemic lupus in the absence of steroid therapy. Steroids do not play an important role in the treatment of gout, so possibly the coagulation abnormalities associated with hyperuricemia rather than steroids contribute to the development of bone necrosis.

We therefore came to regard femoral-head necrosis as a skeletal expression of a systemic disease, or diseases, which by a variety of different events may result in sludging, thrombosis, or hemorrhage in an area of very susceptible blood supply.

REFERENCES

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