# OSTEONECROSIS

## Cape wine as an aetiological agent

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## INTRODUCTION

Ischaemic necrosis of bone, particularly of the femoral head appears to be an increasing cause of musculoskeletal disability in relatively young people (Hungerford 1981). The disease is usually progressive, resulting in the destruction of major weight-bearing joints requiring arthrodesis or arthroplasty. A decade ago it was hoped that joint replacement would solve most of these problems, however, failure of such arthroplasties have often been associated with catastrophic consequences (Chandler 1979).

Despite improvement in design, materials and methods of fixation the unsolved problem remains how to achieve longevity with hip replacement in the young and active patient (Onnerfalt 1992). For such a patient there is still no implant with proven life-long durability. Cementless designs have not provided the predicted results and have exposed new problems and failures. At present although a satisfactory result can be expected in >90% of patients undergoing hip replacement (Solomon 1992), the price of failure is high and second or third operations (revisions) give progressively poorer results (Kavanagh 1985 and Pellicci 1985).

In addition to improving implant design, it is necessary to identify conditions that cause the pathology and attempt to modify these so that the pathological cascade can be avoided. Alcohol abuse has been clearly identified as an associated factor predisposing to non-traumatic osteonecrosis (Jones 1971, Hungerford 1978, and Schnitzler and Solomon 1984), although no causative ingredient has been delineated and the relationship to malnutrition has not been clarified.

Osteonecrosis of the femoral head is a relatively common problem in the Western Cape. Van Vuuren (1984) investigated the radiological changes in the femoral head, neck and trochanter of 493 farm labourers with an age range of 19 to 71 years. All the individuals had received a natural white wine with an ethanol content of 10 volumes percent as part of their conditions of service. The known minimal volume of ethanol taken each day varied from 35 to 150 millilitres. The period of intake ranged from 1 to 55 years. There were 5 individuals with established changes of femoral head necrosis and all of them were symptomatic. In addition there were 69 individuals who had radiographic changes consisting of one or more lucent areas surrounded by sclerosis in the femoral head, neck and greater trochanter which were thought to be related to the ultimate development of avascular necrosis. In these patients there was no specific relation to age, frequency and volume or duration of ethanol intake. However, in the group whose minimal daily consumption was 110 millilitres there was a significant increase in radiological changes.

Osteoporosis in chronic alcoholics has been well documented. Saville (1965) showed the mean bone weight of alcoholic men and women to be significantly different from normal individuals. Endocrine disturbances and calcium deficiency (due to either decreased intake of increased loss) were suggested as possible mechanisms for the development of osteoporosis in alcoholics. Tintera (1949) postulated hypofunction of the pituitary adrenal system to be a factor producing osteoporosis in chronic alcoholics but this has not been confirmed.

Schnitzler (1984) compared the bone morphometric findings of 19 heavy drinkers with those in 43 non-drinkers. It was noted that chronic alcohol abuse lead to reduced mean trabecular bone volume and thickness. The extent of mean bone formation was the lowest in the alcohol group. In this group the mean bone resorption was the highest. Normally there is a close association between bone resorption and bone formation (the "coupling" effect). Excessive alcohol consumption seems to cause decoupling of these two events, possibly through some toxic effect either on the osteoblasts or on events in the "reversal phase" which links resorption to subsequent bone formation. In none of the patients in this series were there changes to suggest frank osteomalacia. Mild " mineralization failure" was however noted and this could be attributed to defective osteoblastic function.

## VASCULAR ANATOMY

Osteonecrosis or bone death is always due to ischaemia, or more precisely, to a disparity between the oxygen need of the bone cell and the ability of the local circulation to supply that need. As with infarction anywhere else, this can be brought about by interruption of the arterial supply or by occlusion of the venous drainage resulting in stasis and gradual oxygen starvation.

The head of the femur derives its blood supply from three main sources:

1. Artery of ligamentum teres,
2. Retinacular vessels, and
3. The nutrient artery.

## ARTERY OF LIGAMENTUM TERES

The artery of ligamentum teres usually arises from the deep or lateral branch of the obturator artery, although it may occasionally originate from the medial circumflex of the profunda femoris. The vessel enters the hip joint by passing under the transverse ligament into the cotyloid notch and travels along the ligamentum teres to the fovea capitis where it penetrates into the head of the femur.

THE CIRCULATION IN THE ADULT HIP - Strange, 1965

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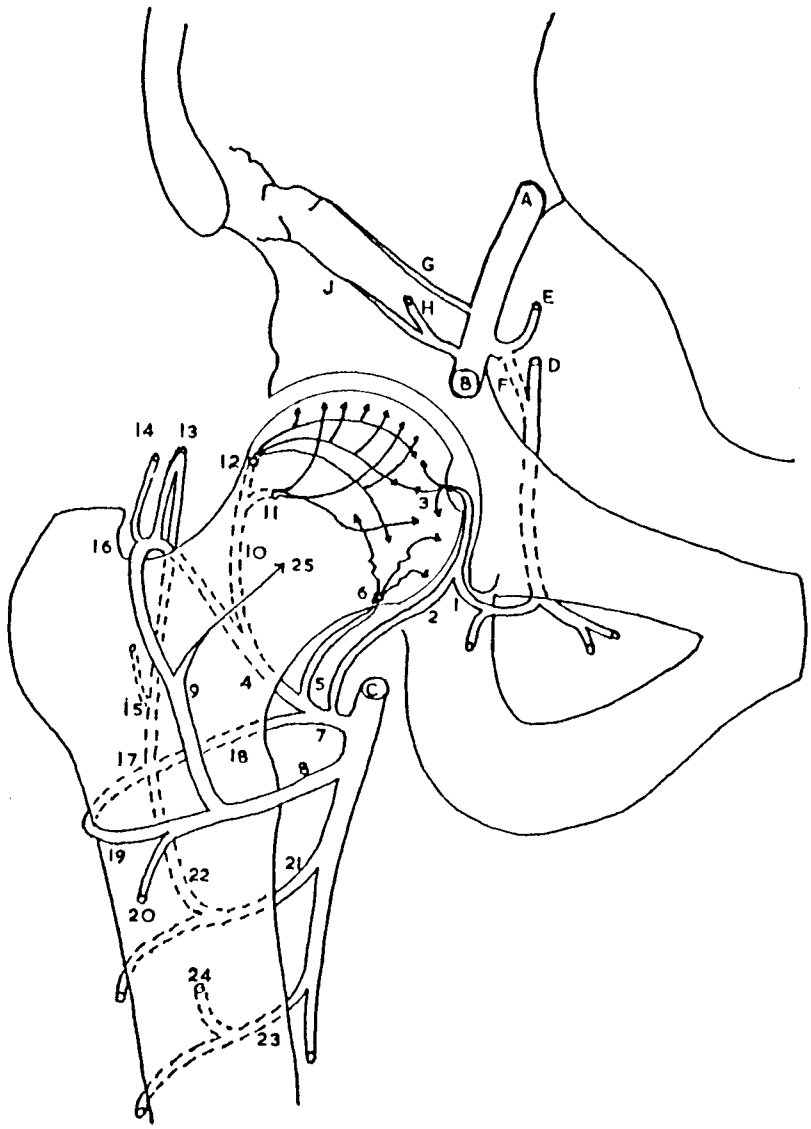


A. External iliac artery.
B. Common femoral artery.
C. Profunda femoris artery.
D. Obturator artery.
E. Deep epigastric artery.
F. Aberrant obturator (30 per cent).
G. Deep circumflex iliac.
H. Superficial epigastric.
J. Superficial circumflex iliac.

1. Origin of foveal artery from lateral branch of obturator.
2. Origin of foveal artery from medial femoral circumflex.
3. "Medial epiphyseal" branches of foveal.
4. Ascending branch of medial femoral circumflex.
5. Postero-medial retinacular branch of medial femoral circumflex.
6. "Inferior metaphyseal" branches of postero-medial retinacular.
7. Medial femoral circumflex.
8. Lateral femoral circumflex.
9. Ascending branch of lateral femoral circumflex.
10. Postero-lateral retinacular branches of medial femoral circumflex.
11. "Superior metaphyseal" branches of postero-lateral retinacular.
12. "Lateral epiphyseal" branches of postero-lateral retinacular.
13. Inferior gluteal (digital branch).
14. Superior gluteal (deep division).
15. Anastomotic branch of sciatic.
16. Digital anastomosis.
17. Cruciate anastomosis.
18. Transverse branch of medial femoral circumflex.
19. Transverse branch of lateral femoral circumflex.
20. Descending branch of lateral femoral circumflex.
21. First perforating artery.
22. Ascending branch of first perforating artery.
23. Second perforating artery.
24. Nutrient artery of femur.
25. Occasional anterior retinacular.

The vessel is very variable in size in about 40% of hips, while in 60% its size is fairly constant and its supply to the femoral head limited to a circumfoveal sector comprising approximately 10% of the femoral head (Strange, 1965).

## THE RETINACULAR VESSELS

The retinacular vessels form two main groups viz. postero-medial and postero-lateral, which arise separately from the medial circumflex of the profunda femoris. They may obtain part of their blood at times from the vessels which take part in the anastomotic network viz. the superior and inferior gluteal and ascending branches of the lateral circumflex and perforating vessels. This arrangement could allow for a continuous supply in the event of any one or more of these vessels being temporarily obliterated either in the extreme of joint range or from compression by muscular contraction, or possibly from prolonged sitting with pressure on the back of the femoral neck.

The postero-lateral vessels are the most constant and play by far the most important role in the blood supply to the femoral head.

The retinacular vessels, as their name implies, ascend the neck of the femur in the reflected retinacular fibres of the capsule, leaving them where they terminate to emerge under the synovial membrane in the upper part of the neck. There they are usually spiral in shape. Shortly before the margin of the articular surface, they enter foramina in the cortex and reach the interior of the neck. The postero-lateral retinacular vessels are further subdivided into superior metaphyseal and lateral epiphyseal branches (Trueta and Harrison, 1953). The superior metaphyseal vessels come off the postero-lateral retinacular trunk a little lower on the neck and perforate the cortex at right angles, curving upwards towards the underside of the old epiphyseal plate (ie. the 'ghost line' of the old epiphyseal plate).

The postero-medial retinacular arteries enter under the most proximal part of the neck and spiral up towards the inner part of the epiphyseal plate where they intermingle with the superior metaphyseal branches and anastomose with them.

Even in the adult the epiphyseal plate constitutes a partial watershed between epiphyseal and metaphyseal circulations. It is penetrated by relatively few spiral interconnecting vessels which are insufficient for the two groups to be described as freely communicating.

NUTRIENT ARTERY

The nutrient artery usually arises from the second or third perforating branch of the profunda femoris and enters the posterior aspect of the shaft of the femur in its upper one third. Its connections with the vessels of the femoral neck are small and apparently of secondary importance.

There is no evidence that the nutrient artery extends its supply to the metaphyseal region (Tucker, 1949), and may therefore play a negligible role in the femoral head blood supply.

## CAPILLARY BED

The capillary arrangement in the head and neck of the femur varies with the site. In the subchondral zone of the articular surface, the capillaries run vertically up to the cartilage, turn and pass immediately under it for a short distance and then turn away again. The arrangement in relation to the bone marrow differs for red and yellow marrow. In older persons the neck and part of the femoral head contains red marrow but the rest of the head fatty marrow. In the former the blood vessels end in anastomosing sinusoids forming a prolific capillary meshwork about each lobule of blood forming marrow. These sinusoids comprise blood cavities many times the size of ordinary capillaries and yet have walls of no greater thickness. In the fatty marrow, the normal pattern of a capillary bed is reproduced with the addition of short conical dilatations of the vessels at their points of junction (Strange, 1965).

REGIONAL ANASTOMOSIS

Until the age of about ten years there is no anastomosis between the various groups of vessels supplying the femoral head; each group has its corresponding return veins which accompany the arterioles closely and may spiral around them. As anastomoses develop it becomes possible for blood entering the head through one system to drain along the veins of another. Drainage from the metaphysis in the growth period is via the superior metaphyseal, inferior metaphyseal and through the medullary connections into the vessels of the lower neck. After the first few months of life there is no drainage from the epiphysis into the metaphyseal vessels except for a small and diminishing exchange in the inferior metaphyseal zone.

Despite the generalised anastomotic arrangement in the adult neck, there is still a tendency for crossed return to be less free than homologous draining. But the connection is certainly very considerable and allows for alternative venous return routes when necessary. It still appears doubtful whether any one set of veins can adequately drain the whole femoral head.

# LITERATURE REVIEW

## AETIOLOGY

Although bone death has long been recognised as a complication of osteomyelitis and certain fractures, aseptic osteonecrosis in the absence of injury was considered unusual before the 1960's (Chandler, 1948; Freund, 1926; Moseley, 1953 and Phemister, 1940). Since then however the condition has been recognised fairly commonly.

The increased reported incidence can be attributed to more cases being diagnosed. This is a heterogenous condition which occurs in many different diseases. The list of conditions (pages 18-20) associated with ischaemic osteonecrosis is long and the aetiologic links are sometimes tenuous.

Most cases of non-traumatic osteonecrosis were at first considered idiopathic, however definitive associations were soon identified. However these pathologic conditions are probably responsible for only a small percentage of cases of osteonecrosis.

Sickle cell disease is the exception, being the principal cause of osteonecrosis in some African countries (Kabakale, 1972). McCallum et al (1970) in their series showed that sickle cell disease accounted for 19% of avascular necrosis of the femoral head.

In the 1950's two remarkable pathologic associations were observed for the first time:

1. Systemic Lupus Erythematosus
   Dubois and Cozyn 1960, and
2. Corticosteriod therapy
   Pietrogrande and Mastromarino 1957,
   Heimann and Freiberger 1960.

In the years that followed, the involvement of corticosteroid therapy was fully documented and elucidated, but the reported incidence varied from 12% to more than 30% of the total incidence of non-traumatic avascular necrosis of the femoral head.

Furthermore, osteonecrosis complicating systemic lupus erythematosus was attributed to corticosteroid therapy in most cases, although Dubois and Cozen (1960) noted that some cases developed osteonecrosis before initiation of corticosteroid therapy. Corticosteroids were also implicated in avascular necrosis of the femoral head secondary to renal transplantation, first reported by Jones (1965) and subsequently by Cruess (1968).

A history of previous corticosteroid treatment is noted in 30 to 50% of female patients with avascular necrosis of the femoral head. Corticosteroid induced hip necrosis is bilateral in more than 50% of cases and often involves multiple locations. It is also reportedly more severe than idiopathic osteonecrosis. These peculiarities viz. bilaterality, multiple site involvement and severity are even more evident in osteonecrosis associated with systemic lupus erythematosus (SLE). In twenty eight cases studied by Zizic et al (1985), twenty seven were females and twenty six had more than one bone affected. Kalla (1986) reviewed 185 patients with SLE and found 13 (7%) to have avascular necrosis. All were women aged between 17 and 50 years, and all had received corticosteroid therapy at some stage of the disease. The mean total dose of corticosteroid therapy was 15 g (range 3.2 - 47.0 g) and the mean duration of therapy was two years (range 4 months to 4 years).

The relationship between corticosteroid dose and the advent of osteonecrosis remains unclear. In a review by Fisher and Bickel (1971), the shortest period of treatment with corticosteroids was thirty days at a dose of 16 mg/day prednisolone. However in 1982, Anderson et al presented a case of multiple joint necrosis after 700 mg of prednisolone was given over seven days.

Alcohol abuse was first implicated as a probable risk factor as early as 1962 by Massias et al. Its aetiologic role was confirmed over the ensuing years, with a frequency varying from 10 to 42% (Zinn, 1971).

Hyperuricaemia was found frequently in all series of avascular necrosis of the femoral head; the incidence varied from 16 to 30%. Jacobs (1978) in his series of 58 patients with hyperuricaemia and osteonecrosis noted that only 18 patients were known to have clinical gout. Thirty two patients had other coexistent disorders also known to be associated with osteonecrosis, notably alcoholism in 20 patients and steroid therapy in 14. Gouty subjects tend to be hyperlipidaemic, in common with alcoholics and steroid treated patients. Hyperlipidaemia was noted in 33 patients and there was evidence of liver dysfunction in 25.

McCallum (1970) observed definite uric acid crystals in the synovium of the hip in twelve of twenty nine patients with avascular necrosis of the femoral head, but no crystals were noted in any of fifty three control individuals.

Lequesne et al (1961) were the first to draw attention to the pre-beta lipoproteins in non-traumatic osteonecrosis. The association was subsequently confirmed by others (Roux et al, 1974). These lipid abnormalities are also found in patients with obliterative arteritis, diabetes mellitus and atheromata. Arlet et al showed a probable relationship between obliterative arteritis and osteonecrosis (1975) and between pregnancy and osteonecrosis (1982).

Ficat and Arlet (1980) have listed the conditions associated with osteonecrosis as definite and probable.

CONDITIONS ASSOCIATED WITH OSTEONECROSIS

I DEFINITE CAUSES

| | |
|---|---|
| Trauma: | Fracture of femoral neck<br>Proximal femoral epiphysiolysis<br>Dislocation of the hip<br>Epiphyseal compression<br>Vascular trauma |
| Post irradiation necrosis | |
| Haemoglobinopathies: | Sickle cell disease<br>Haemoglobin S/C haemoglobinopathy<br>Haemoglobin S thalassaemia<br>Polycythaemia |
| Caisson disease: | Dysbaric osteonecrosis |
| Local Infiltrations: | Gaucher's disease<br>Neoplastic conditions |

II PROBABLE CAUSES

| | |
|---|---|
| Hypercortisolism: | Corticosteroid administration<br>Cushing's disease |
| Gout | |
| Bone dysplasia | |
| Lipid disturbances | |
| Alcohol abuse | |
| Connective tissue disease: | Systemic lupus erythematosus |
| Osteoporosis | |
| Osteomalacia | |
| Pancreatic disease | |
| Hepatic disease: | Hepatitis<br>Hepatoma |
| Diabetes mellitus | |
| Fat embolism | |
| Obesity | |
| Oestrogen therapy | |
| Organ transplantation | |
| Chronic renal disease | |

In the definite associations effect follows cause in a temporal sequence that leaves little doubt as to their linkage. The list of probable associations is more controversial. The association is established by the greater incidence of osteonecrosis seen in certain conditions. In many cases, particularly corticosteroid therapy and alcohol abuse, the mechanism by which the necrosis is produced is in dispute.

Jones (1989) reported miscellaneous associations in the aetiology of osteonecrosis. These include:

Neuropathic arthropathy

Carbon tetrachloride poisoning

Congenital malformations

Clotting defects

Convulsive disorders

Diabetes mellitus

Endocarditis

Hepatitis

Histiocytosis

Myxoedema

Pancreatitis

Thrombophlebitis

EPIDEMIOLOGY

Japanese orthopaedic surgeons conducted an extensive epidemiologic survey of the prevalence of osteonecrosis since 1974. Ninomiya (1989) estimated that non-traumatic avascular necrosis of the femoral head occurred in some three thousand adults during 1988 alone (ie. new cases diagnosed). Of these cases the associations were as follows:

1. 34.7% were due to corticosteroid therapy,
2. 21.8% following alcohol abuse, and
3. 37,1% were considered to be idiopathic.

These findings are similar to those of Jacobs (1978), who reviewed the epidemiology in New York, USA.

## PATHOGENESIS

Despite the dissimilarity of the pathogenetic disease entities, the clinical picture and basic pathological process, although poorly understood, appears to be the same. The popular theories to account for cell necrosis are:

A: Ischaemia due to:

1. Occlusion of arterioles by intravascular fat emboli;
2. Compression of the vessels by accumulation of marrow fat stores;
3. Intraosseous hypertension; and
4. Vascular damage due to microfractures which occur in osteopenia.

B: Direct toxic effect of alcohol on bone.

These would all lead to compromise of the microvascular circulation, anoxia, further rise in intraosseous pressure, metabolic disturbance and finally osteocyte necrosis.

Certain sites appear to be particularly vulnerable to osteonecrosis viz. the femoral head, the femoral condyles, the humeral head and the talus. In each of these sites the necrotic segment appears immediately below the load-bearing articular surface of the bone end. The frequent involvement of the femoral head has been attributed to the endarterial system of blood supply to this region (Sevitt 1965).

In the absence of a collateral supply, blockage or disruption of the small vessels rapidly leads to ischaemia. It has been estimated that bone cells die after 12 to 48 hours of anoxia and marrow fat cells after 5 days (Kenzora 1969 and Rosingh 1969).

In aseptic non-traumatic osteonecrosis, the process of repair differs with the causative agent and the amount of functional stimulation to which the part is subjected during the reparative period. It also differs from that seen in osteonecrosis secondary to infection. Necrosis en masse produced by severe infection is nearly always followed by a fibroblastic and a phagocytic reaction which usually results in complete absorption of the dead bone if the area is small, or in sequestration if it is large (Phemister, 1992).

The fate of bone which undergoes aseptic necrosis as a result of circulatory disturbance varies considerably according to the environment of the necrotic area. If the necrotic bone is attached to and directly continuous with living bone, there is ingrowth of vessels and of fibrous and osteogenic tissues from the living into the necrotic area. There is usually survival of unossified osteogenic elements in the periphery of the area that has had its circulation interrupted.

By the process of creeping substitution the dead bone is gradually resorbed and replaced by new bone, so that in the course of months to years the necrotic area is more or less completely transformed into living bone. Whether the amount of new bone formed equals the amount of bone which died depends largely on the amount of osteogenic elements surviving in its periphery, and the extent of contact with adjacent live bone.

When both of these are extensive, there may be complete replacement of the dead bone by new bone: but when limited, bone resorption may be greatly in excess of bone formation, so that incomplete replacement results. Bone is then formed that is less dense than the original and shows varying degrees of cavitation.

Functional stimulation also plays an important role in the rate and degree of transformation. In general the greater the degree of function, the greater the rate and degree of transformation into new bone. If the necrotic bone is largely or wholly intra-articular and extensively bordered by articular cartilage, the attachment to the surrounding soft parts will be markedly limited and chances for revascularisation and transformation will be greatly reduced.

Aseptic osteonecrosis following thrombosis or embolism has rarely been reported. Axhausen reported a case which was classed as multiple anaemic infarction of bones, but Streptococcus longus anhemolyticus was cultered from the lesions. Consequently it is incorrect to refer to this as aseptic necrosis of bone. Aseptic necrosis has been produced experimentally by injection of small aseptic emboli into the femoral artery. The infarcts formed in the ends of the shafts and rarely comprised a large part of the diaphysis, but epiphyseal necrosis was not produced. A marked osteoblastic reparative reaction developed about the necrotic bone which was rapidly replaced by new bone by the process of creeping substitution (Phemister, 1992).

Specimens obtained by core biopsy in precollapse cases have allowed description of early marrow lesions such as necrosis of haematopoietic cells, haemorrhages, and reticular eosinophilic atrophy of the lipocytes. Investigators have been able to demonstrate that these lesions can occupy a large area before and/or underneath the sequestrum (Ficat, 1980). In most cases the first visible lesions occur in the marrow and these are diffuse and spotty, and bone marrow involvement precedes osteocytic lesions (Kenzora, 1978).

The subchondral fracture is usually located in the subchondral dead bone. In the triangular sequestrum, the dead trabeculae lose all their osteocytes but retain their architecture. In addition the bone marrow tissue may become an amorphous mass without recognisable cellular nuclei or cellular structures except occasionally ghosting of the lipocytes (Jacqueline, 1971). The dead tissue of the sequestrum is usually in continuity with the concave zone of repair, including fibrovascular proliferation and active bone resorption. A second fracture site occurs at the inferior aspect of the sequestrum ie. at the junction of dead and live bone.

The classic radiological features of idiopathic necrosis of the femoral head are increased density, subchondral crescent fracture and collapse of the femoral head, but these are all late manifestations of the disease. The early changes were studied by Solomon (1981) in thirty four patients receiving high dose corticosteroid and in eleven patients with avascular necrosis of the femoral head attributed to alcohol abuse.

Recognising that the earliest pathophysiological changes occur in the asymptomatic patient with no radiographic changes, Solomon studied the unaffected side in patients with proven contralateral osteonecrosis of the femoral head.

The earliest pathologic changes were a relative increase in cancellous bone fat at the expense of myeloid tissue, swelling and necrosis of the fat cells, and variable areas of cell death in the trabeculae. All of these were fairly widespread throughout the proximal femur. Intraosseous pressures were raised, suggesting the presence of venous stasis. Fat cell size was measured in undistorted femoral heads with osteonecrosis and in a comparable series with osteoarthritis. There was a significant increase in fat cell size and a virtual absence of vascular sinusoids in histiologic sections from those with osteonecrosis. Solomon proposes that osteonecrosis occurs as a sequence of the following events:

- Fatty accumulation and replacement of myeloid tissue
- Compression of vascular sinusoids
- Venous stasis
- Ischaemia
- Fat necrosis
- Bone necrosis.

Crues implicates regional anoxia as the cause for lipocyte hypertrophy.

## CLINICAL FEATURES

The patient complains of pain in the hip which progresses over a period of years, and on examination, walks with a limp and may have a positive Trendelenburg sign. The thigh is wasted and the leg may be short. Movements are restricted, particularly abduction and internal rotation. The early stages in this chain of events are clinically asymptomatic and produce no radiologic abnormality.

With magnetic resonance imaging this preradiologic stage of the disease may be diagnosed. By the time the diagnosis of osteonecrosis is made radiologically, the condition has been present for months or even years. The very hallmark of the clinical disorders viz. increased density of the femoral head on roentgenogram is a manifestation of repair; new bone formation upon the dead trabeculae producing an increase in bone mass. The increased bone density of the sequestrum is relative ie. surrounding vascularized bone becomes osteopenic due to eg. disuse while the avascular does not.

Ficat (1985) suggested a staging for avascular necrosis based on radiological changes.

Stage 1 Roentgenograms are normal or may show minimal osteopenia.

Stage 2 Roentgenograms demonstrate a normal cartilage space and sphericity of the femoral head. The intramedullary portion of the femoral head has a wedge-shaped area of sclerosis in the superior weight-bearing portion with patchy osteopenia and osteosclerosis.

Stage 3 The radiolucent crescent sign and early collapse may be apparent.

Stage 4 Characterized by loss of contour of the femoral head and degenerative changes in the hip joint.

Magnetic resonance imaging can depict early avascular necrosis of the femoral head in asymptomatic and roentgenographically normal patients. Kokubo (1992) divides the abnormalities seen on MRI into five patterns:

Type A Diffuse decreased signal intensity.

Type B Peripheral areas of low signal intensity.

Type C Band-like areas of low signal intensity.

Type D Multiple spotted areas of low signal intensity.

Type E Distal areas of low signal intensity.

It was noted that MRI was more reliable than radionuclide scanning for detecting the femoral head at risk of subsequent segmental collapse. In particular, a band-like area of decreased signal intensity seems to be a significant indicator of subsequent segmental collapse.
MRI reflects soft tissue (ie marrow changes) whereas the technetium radionuclide bone scan is a hard tissue test reflecting bone formation.

## THE "COMPARTMENT SYNDROME"

Normally the resting pressure in the greater trochanter of the femur is 10-24 mmHg and injection of 5mls of saline (the stress pressure) does not provoke hypertension (Figure 1). Since 1973 Hungerford has been using the measurement of bone marrow pressure as a method of detecting bone ischaemia in the preradiologic and even preclinical stages. He has shown a high incidence of elevated bone marrow pressure in the early stages of bone ischaemia. These findings are not restricted to the hip, but have been demonstrated in the knee and shoulder as well. Hungerford (1981) measured the bone marrow pressure of the contralateral uninvolved hip in twenty seven patients who had proven unilateral ischaemic necrosis of the femoral head. Seventeen hips demonstrated abonormal bone marrow pressures (Figure 2), while in thirteen patients bone ischaemia was subsequently confirmed histologically.

BONE MARROW PRESSURE - Hungerford, 1981.

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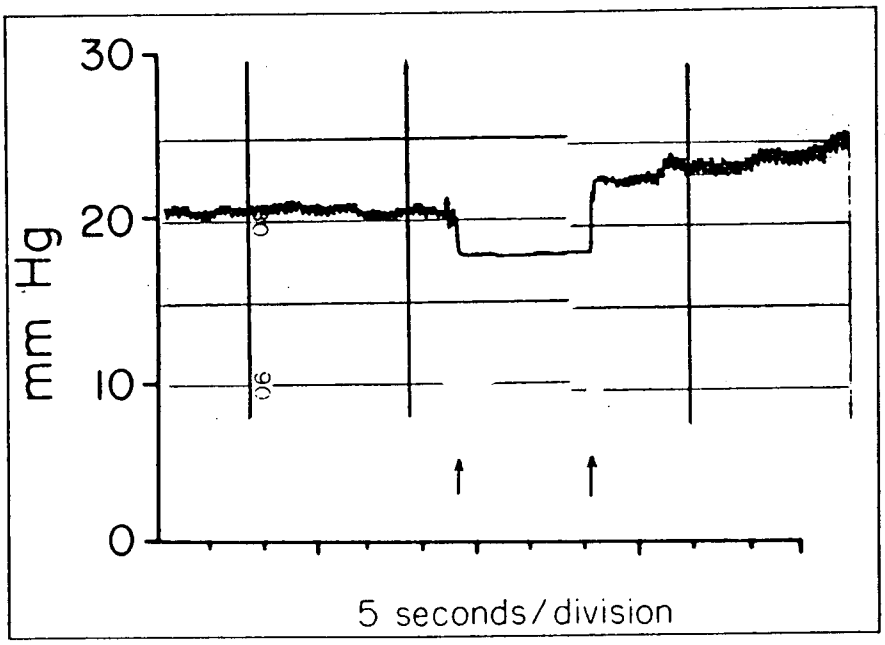
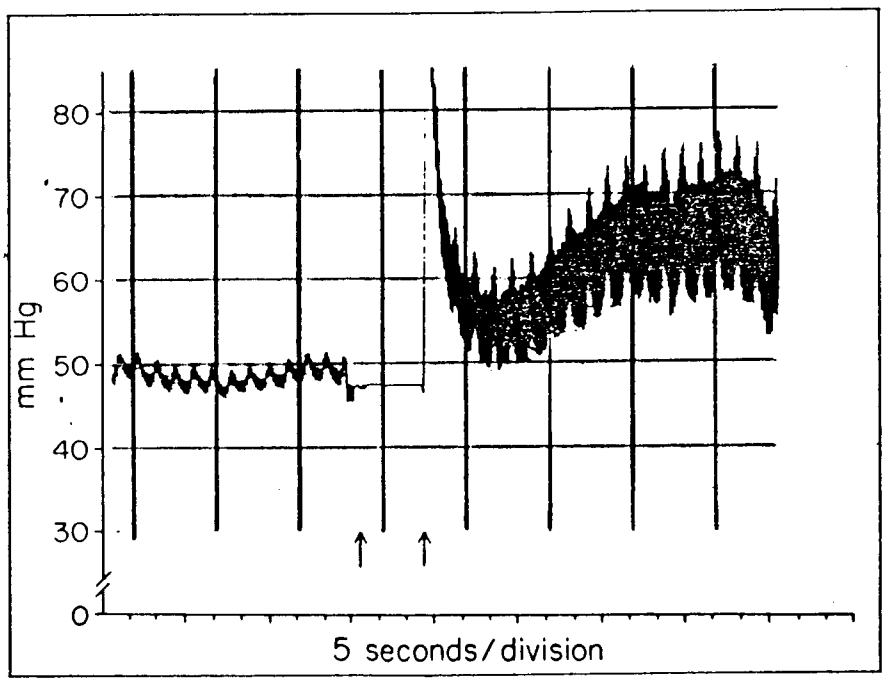
Figure 1




Normal bone marrow pressure does not exceed 30 mm Hg and shows pulse pressure and changes with respiration. Injection of 5 ml. of saline (between arrows) does not provoke intraosseous hypertension.

Figure 2




Bone marrow pressure in early avascular necrosis of femoral head showing both elevated baseline pressure and hypertensive response to saline loading (between arrows).

Solomon confirmed these findings when he investigated five 'unaffected' femoral heads in patients with avascular necrosis of the contralateral hip. He noted raised resting and stress pressures in these femoral heads. He also noted an interesting finding in the pressure tests of the radiographically diagnosed osteonecrotic femoral heads. Excessively high pressures were still present as long as the femoral head was intact, but once the head had fractured or collapsed the injection of saline no longer increased intraosseous pressure. The region had in a sense decompressed itself and in some cases he found that saline injection actually produced a fall in pressure. It has therefore been hypothesized that bone behaves like a closed compartment and that avascular necrosis of the femoral head is a slowly developing compartment syndrome. The end stage of this syndrome is bone death and mechanical failure of bone. The characteristic anatomical localization of the failing segment is on the basis of the biomechanics of weight-bearing on the femoral head and not on the basis of circulatory insult or anatomy ie. the area of the head involved relates to where the stresses are the greatest and in the hip this is the antero-superior aspect of the femoral head. It is postulated that the cycle is similar to that of other compartment syndromes.

Increasing compartment pressure produces an outflow obstruction by collapsing the thin walled low pressure venules and veins, thereby increasing vascular resistance. Without a change in extraosseous inflow pressure, flow would fall. The ischaemia is worsened and extra-vascular intraosseous pressure rises. If decompression takes place during the ischaemic phase, rather than after necrosis, the process is potentially reversible.

EXPERIMENTAL STUDY

Two theories for the development of osteonecrosis in alcohol abuse have been advanced:

1. The fat embolism theory which postulates the occurrence of intravascular fat globules associated with hypertriglyceridaemia and fatty infiltration of the liver (Jones 1971); and
2. The marrow steatosis theory which is based on the observation that marked fatty infiltration of the marrow could cause pressure upon the sinusoids with vascular stasis leading to ischaemia (Hungerford 1979 and Solomon 1981).

At UCT medical school a study was undertaken to assess the effect of alcohol consumption and malnutrition on bone and liver morphology in the rat.

We would have liked to propose that there may be a substance other than the ethanol alone in wine that causes the bony changes to develop, but this still needs to be demonstrated. The alcoholic beverage used in this study was a cheap local semi-sweet wine and the high sugar content in combination with the ethanol in an undernourished rat may be the prerequisite to the development of bony changes.

## METHODOLOGY

Twenty four Long Evans rats were divided into three groups of eight each:

Group A consumed water,

Group B consumed an undiluted semi-sweet wine, and

Group C consumed 10% ethanol (diluted in water).

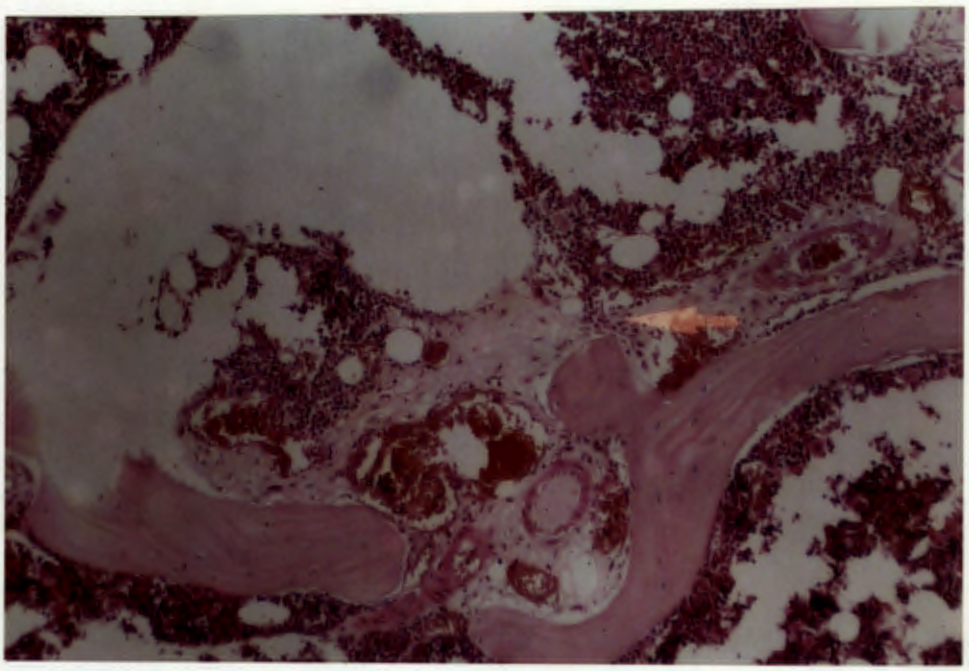
In each of the groups four rats received a reduced diet of 20 g/day rat chow and four a normal diet of 50 g/day. The daily fluid consumption and the weight of the rats were recorded each week. Six rats (two from each group) were sacrificed at successive intervals of three months. It is unfortunate that I was not able to perform a Girdlestone type excision arthroplasty in order to assess the histological changes of the femoral head. This would have allowed reassessment of the opposite hip at a later stage. The request to perform such surgery had been refused by the University ethics committee.

The rats were given a lethal dose of anaesthesia and the femora were removed and cleaned of all soft tissue. The excised femoral head was fixed in 10% formal-saline for at least 48 hours following which it was decalcified in Christenson's solution (Drury 1973) and transferred to 70% alcohol. The decalcified bone was then embedded in paraffin wax. The specimens were sectioned using a microtome (6 um) and attached to a slide with adhesive. Once dry, the sections were stained with Erlich's haematoxylin and eosin. The liver was biopsied and sections were stained with Erlich's haematoxylin and eosin. The liver and bone specimens were assessed by a pathologist who was blind to the group of their origin.

RESULTS

At three, six and nine months none of the rats showed any bony or liver changes. At twelve months one rat from group B (fed on a 20 g/day diet and wine) showed bony (figure 3) and liver changes (figure 4). The bone marrow was replaced by fibrous tissue and osteoblastic rimming was noted.

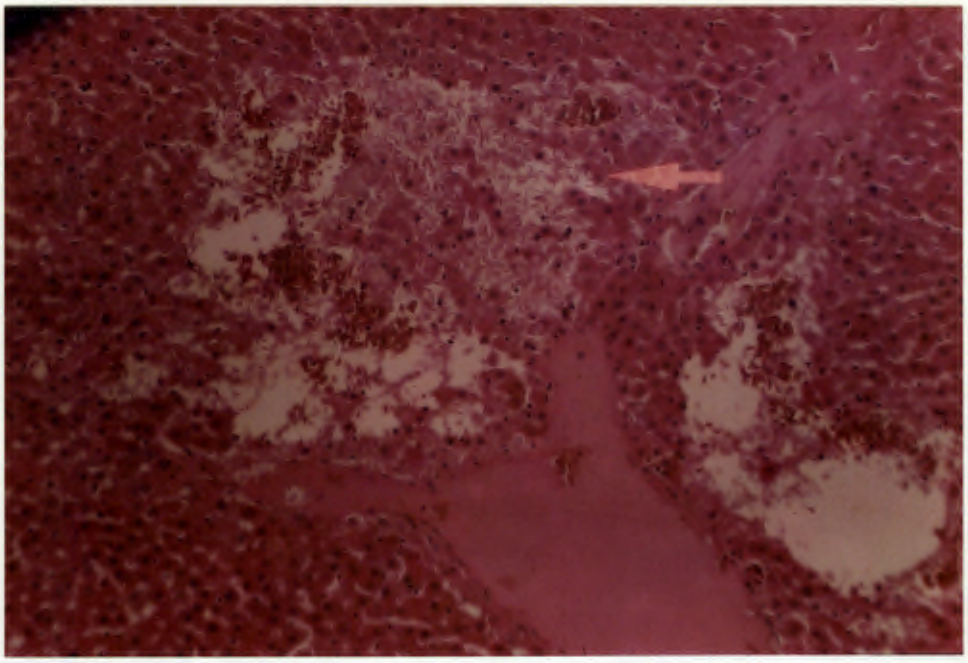
Figure 3



The section of bone shows viable lamellar bone and marrow. There is evidence of fatty accumulation and early fat necrosis. Areas of fibrous replacement were also noted.

The liver biopsy from the same rat showed fatty degeneration.

Figure 4

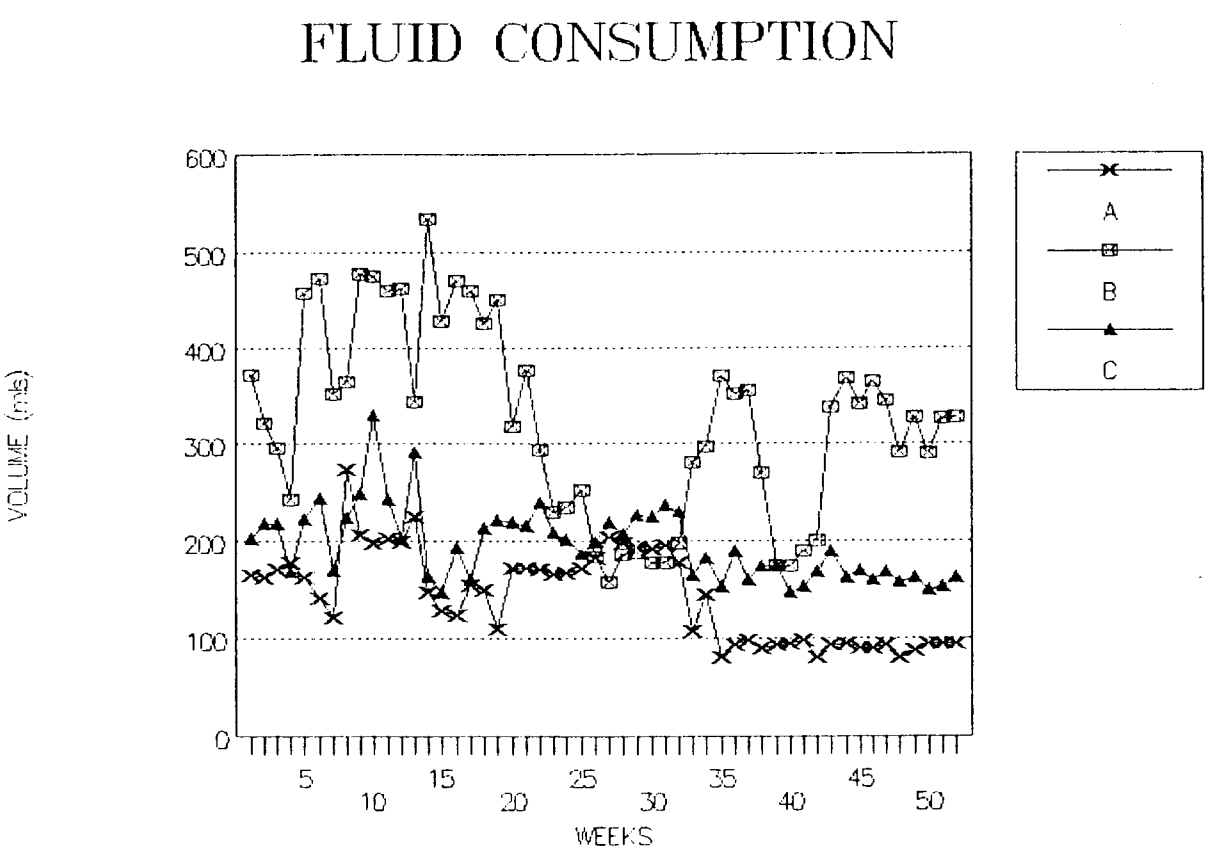


The liver architecture was normal. Areas of fatty degeneration were noted.

One rat from group C (fed on 50 g/day diet and 10% ethanol) sacrificed at twelve months showed liver fatty change, but no bony changes.

Wine consumption by group B exceeded the ethanol consumption by group C, which exceeded water consumption by group A (figure 5). This is expected because of the addictive nature of alcohol as well as its diuretic effect (Saville 1965).

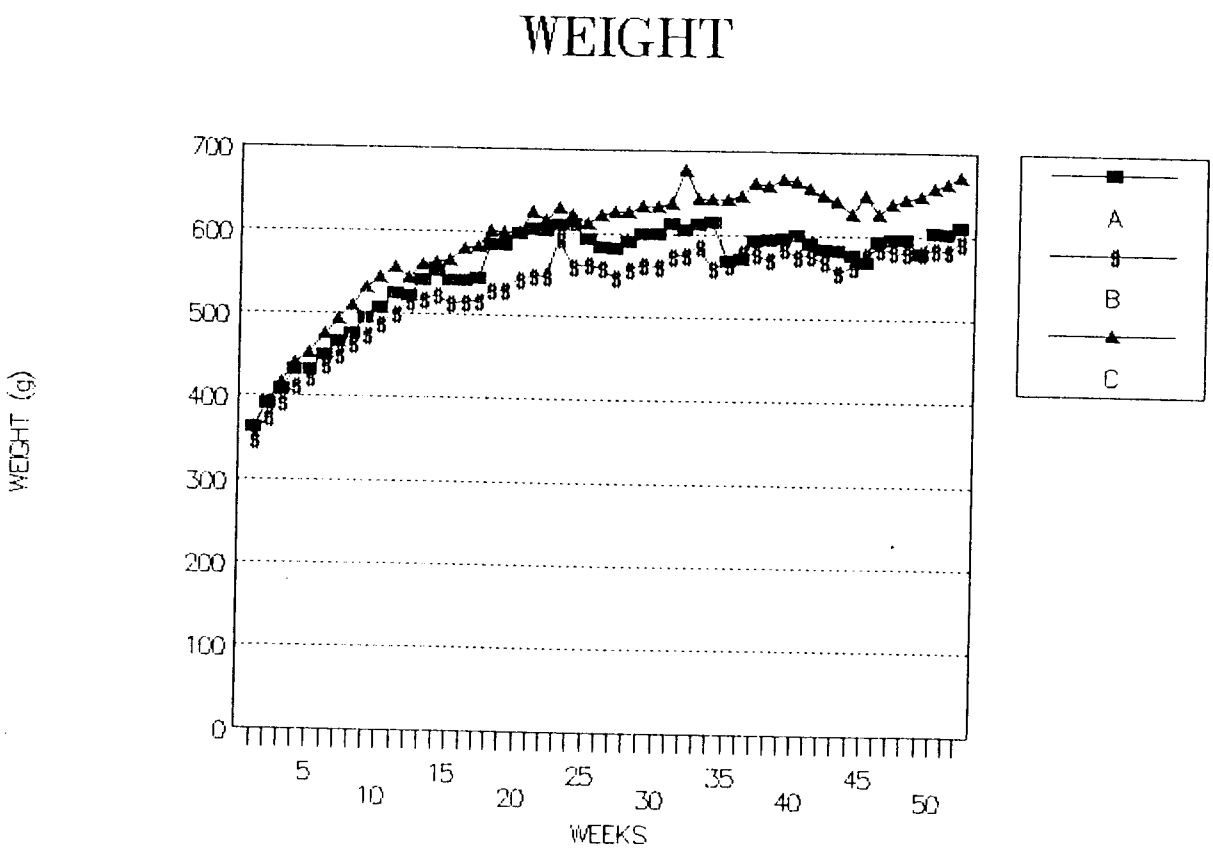
Figure 5




The graph depicts fluid consumed by the rats in the various groups (A drank water, B wine and C ethanol).

All rats gained weight steadily over the first six months and remained stable over the next six months (figure 6). This represents maturation from childhood to adulthood (Baker 1980).

Figure 6




The graph depicts weight gain by the rats in the various groups.

## DISCUSSION

A comparison of the alcohol and sugar content of the various alcoholic beverages (table 1) shows a signicantly higher alcohol content in whiskey and brandy and a significantly higher sugar content in sweet to semi-sweet wine, muscadel and port.

Table 1

Comparison of the alcohol and sugar content in alcoholic beverages

| | Alcohol (%) | Sugar (g/l) |
|---|---|---|
| Semi-/sweet wine | 12.5 | 15 to 30 |
| Red wine | 12.5 | 1.9 |
| Whiskey | 43 | 0.5 |
| Brandy | 43 | 5 |
| Beer | 6 | |
| Muscadel | 16 to 22 | 140 |
| Port | 16 to 22 | unlimited |

Table 2

Fractionation of the semi-sweet wine used in this study identified the following:

| | |
|---|---|
| ALCOHOL | |
| Total | 10.13 % |
| N Propanol | 29 mg/l |
| Iso Butanol | 14 mg/l |
| Iso Amyl Alcohol | 137 mg/l |
| SUGAR | 15.1 g/l |
| PRESERVATIVE | |
| $SO_4$ | 139 mg/l |
| Aldehyde | 75 mg/l |
| ACID | |
| Total | 4.8 g/l |
| Fixed acid (tartaric) | 4.4 g/l |
| Volatile acid (acetic) | 0.35 g/l |

Data obtained from

The Deputy Director: Liquor control

Department of Agricultural Economics and Marketing.

This must be considered a preliminary study because at commencement of the experiments it was not known how long it would take to see any histological changes in the liver or femoral bone following consumption of wine or ethanol. Six rats were sacrificed at 3 months, six more at 6 months and six at 9 months. This left only 6 rats for review at 12 months. This was unfortunate, but I have learnt that for future studies the rats will be sacrificed after at least 12 months of exposure to these agents. The results of this study are therefore not conclusive because of the small numbers involved.

In a previous study semi-sweet wine was incriminated as the aetiological agent in more than 95% of those patients presenting with osteonecrosis where alcohol abuse was identified as the aetiological agent (unpublished data - Maloon and Learmonth).

It is postulated that rapid absorption of the sugar (in the form of monosaccharides) may result in hyperinsulinaemia and that lipid deposits may then be mobilised during the subsequent hypoglycaemia.

In our study the alcohol content of the fluid consumed by the rats in group B (wine) and group C (10% ethanol) was the same. It should however be noted that the rats in Group B consumed larger quantities of wine and therefore had a greater alcohol intake than the rats in Group C.

The high sugar content of the semi-sweet wine in combination with the ethanol in an undernourished rat may be the prerequisite to the development of bony changes. However, malnutrition was not evident as all rats in this study gained weight adequately. The degree of malnutrition required in combination with an offending agent like alcohol to produce osteonecrosis is not known and this study has failed to provide any further information regarding this. Clearly more work is required to define the relative roles of alcohol and nutrition in the causation of Cape osteonecrosis.

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