SUPPLEMENT TO

CLINICAL AND LABORATORY STUDIES INTO POSSIBLE RELATIONSHIPS BETWEEN ALCOHOL AND MUSCULOSKELETAL DISORDERS WITH EMPHASIS ON RHEUMATOID ARTHRITIS PRIMARY OSTEOARTHRITIS OF THE HIP AND DUPUYTREN'S CONTRACTURE

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INTRODUCTION

This thesis has covered several widely - different fields of study before reaching its final unifying conclusions. Inevitably, to allow the thesis to read better and to avoid irrelevance and repetition, I found it necessary to limit my reports of previous work to those studies pertaining directly to this thesis (except where historical perspectives were helpful). I am extremely - grateful to my Examiners for recognizing this and also for pointing out some important errors and omissions. The purpose of this Supplement is to correct the omissions and errors pointed out by the Examiners and to reply to their comments about the prospective studies. The revisions and discussion of the Examiners' comments are undertaken section by section. To follow the argument it is therefore necessary to read this Supplement in conjunction with the main body of the thesis.

I wish to record my sincere thanks to Professor JP de V van Niekerk, who kept me informed of the progress of the thesis in the later stages of its Examination thus diminishing the anxiety I felt due to the 10,000 km separation between the Examiners and myself. I am also indebted to the staff of the Medical Library at the Royal Berkshire Hospital, Reading who assisted me without complaint during my frantic search for late references.

EXAMINERS' COMMENTS WITH CANDIDATE'S REVISIONS,

CORRIGENDA AND DISCUSSION

SECTION 4.2: OSTEOPOROSIS

Examiner's Comment:

I thought that the review of alcohol and osteoporosis was rather under-researched (all the references are dated 1982 or earlier).

Candidate's Revision:

Dalen and Feldreich (1974) and Dalen and Lamke (1976) confirmed the finding of reduced bone mass in alcoholics by Saville (1965) and Nilsson and Westlin (1973). The mean annual bone mineral loss in alcoholics appears however to be only marginally greater than that of controls (Dalen and Lamke 1976, Posner et al 1977) although consistent in the subjects studied by these workers.

Posner et al (1977) also noted that the bone density of the distal radius in "severe, stable alcoholic cirrhotics" did not correlate with serum 25-hydroxyvitamin D levels. Although these levels were reduced compared with controls they were "sufficient to result in metabolic activity in bone." Others (Lalor and Counihan 1982) have confirmed reduced 25-hydroxy vitamin D levels in alcoholic cirrhotics but the conclusions of Posner et al (1977) do not suggest that these reduced levels are significant in causing "alcoholic bone disease."

Johnell, Nilsson and Wiklund (1982) noted that the rate of bone mineral loss in alcoholics was greater in those who had previously undergone gastric surgery. Bone mineral content was not lower in those with an increased frequency of fractures. Osteomalacia, on the few occasions it was seen on bone biopsy, occurred almost-exclusively in subjects who had previously undergone gastrectomy. Osteoclast activity was significantly-increased regardless of previous gastric surgery.

In another study this group confirmed a non-significant increase in serum parathyroid hormone (PTH) activity in alcoholics which fell with abstinence; they felt that the increased PTH activity may have been secondary to an alcohol-induced calciuresis (De Marchi et al 1984) rather than to a direct stimulation of PTH activity by alcohol (Johnell, Kristensson and Nilsson 1982).

Schnitzler and Solomon (1984) demonstrated considerable diminution of trabecular bone volume and bone formation (but increased bone resorption) in subjects consuming over 80 gm alcohol daily compared with osteoarthritic and femoral neck fracture control subjects. These changes were most-pronounced in heavy drinkers and were independent of abnormalities in liver function tests. Osteomalacia was not seen. The authors proposed that bone changes in alcoholics were due to "uncoupling" of bone formation and resorption.

In summary these studies and those previously discussed in Section 4.2 show that bone mineral content and bone formation is decreased in alcoholics. Bone resorption is increased and osteomalacia is rare. These osteoporotic changes are morphologically-similar to those seen in elderly women (Johnell, Nilsson and Wiklund 1982, Schnitzler and Solomon 1984). Their cause is unknown: Schnitzler and Solomon (1984) and Bikle et al (1985) have reviewed the numerous suggested mechanisms which include

ethanol-induced calcium and magnesium hyperexcretion by the kidney, enterocyte abnormalities leading to calcium and vitamin D malabsorbtion, depression of plasma testosterone, elevation of plasma free cortisol levels and defective bone collagen synthesis. Alcoholic liver disease may not be a prerequisite for the development of alcohol-induced osteoporosis (Johnell, Kristensson and Nilsson 1982, Schnitzler and Solomon 1984).

Possibly alcohol-induced osteoporosis represents the end of a "final common pathway" of several of these imputed mechanisms acting synergistically, different combinations occurring in different individuals. Bikle et al (1985) suggest that this "final common pathway" is an inhibition of bone remodelling by a mechanism independent of changes in calciotropic hormones.

SECTION 4.4.1 (p 28 - 29): CONFUSION OF OA HIP AND ANFH

Examiner's Comment:

On page 28 the Section 4.4.1 deals with avascular necrosis of the femoral head, and here several blatant deficiencies are evident. To start with, the crucial description of the blood supply of the femoral head mentions only the insignificant ligamentum teres and nutrient artery contributions, omitting all mention of the major supply from the retinacular vessels. The ensuing description of the morbid anatomy is naive, failing to mention the well - established zones described in the avascular segment by d'Aubigne. In defence... the thesis is not primarily concerned with avascular necrosis; only two cases were encountered and are dealt with elsewhere in the text. Nevertheless, if a new sphere is entered it should be accurately dealt with.

Candidate's Revision:

The femoral head has its blood supply from three freely - anastomosing sources. The area around the fovea centralis receives a small arterial contribution from the acetabular side of the joint through the ligamentum teres. Terminal branches of the medullary arteries arising distally in the shaft of the femur contribute a further minor supply. The main vascularization of the femoral head is however via the retinacular arteries. These are branches of the medial and lateral femoral circumflex arteries which perforate the femoral cortex just distal to the femoral head. The importance of this supply was detailed by Trueta and Harrison (1953) and corroborated by Judet et al (1955). Both groups emphasised the importance of the lateral epiphyseal artery in the femoral head blood supply; later workers (Crock 1965, Kelly 1968) highlighted the free anastomoses between the various vessels around the femoral head.

In the femoral head the terminal branches of the retinacular arteries are arranged in arcades, running perpendicular to the main stem in a radial fashion toward the articular surface. Communicating branches unite these arch vessels, which sub-branch into ever-smaller arcades "like a series of fountains" (Trueta and Harrison 1953). The importance of these arcades is that they allow adequate blood flow through the smallest vessels despite a graduated decrease in the perfusion pressure toward the periphery of the bone (Brookes 1964). This low - pressure perfusion system is vulnerable to compromise by increases in pressure in the surrounding tissues; the small calibre of the retinacular vessels also renders them vulnerable to obstruction by microemboli. The possible role of these mechanisms in causing ANFH is discussed in the Revised Section 4.4.5.

Interruption of part of the arterial supply characteristically produces a segmental area of bone infarction, widening towards the cartilagenous proximal end of the femoral head. The morbid anatomy of the infarcted segment has been elegantly described by French workers (Merle d'Aubigne et al 1965). Macroscopically, in a frontal section of the femoral head, the avascular lesion is characterised by a hard, white central necrotic core surrounded by a reddish zone, which itself is surrounded by a zone of dense bone. The inferior limit of the lesion is usually near the fovea centralis. Microscopically the articular cartilage overlying this lesion is almost- always found to be alive and indeed is usually thicker than normal. The subchondral bone is necrotic, with scanty osteocytes but normal trabecular architecture. This area corresponds to the hard, white area seen macroscopically. The reddish zone surrounding it is an area of bone destruction or resorbtion, where bone tissue is "nearly completely absent"; fibrosis of the medullary spaces is a notable feature. In this actively - vascular region with numerous blood vessels osteoblasts are seen destroying the trabeculae of the necrotic bone core.

Surrounding these areas is a zone of osteosclerosis and vascular proliferation containing many blood vessels in viable cancellous femoral head bone; new trabeculae are seen at the limit of bone destruction. Merle d'Aubigne et al (1965) comment that the area around the ligamentum teres is usually part of this sclerotic zone.

SECTION 4.4.5 (p 32 - 34): PROPOSED MECHANISMS FOR THE DEVELOPMENT OF ANFH IN ALCOHOL ABUSERS

<u>Examiners' Comments:</u> <u>First Examiner:</u>

Near the end of page 264, under the Section 22.6 "The Way Forward: Possible Future Studies Arising From This Thesis," there appears a fleeting reference to the swollen lipocyte theory. This is the wrong place for the reference and it is grossly inadequate.

Second Examiner:

It was disappointing to find omissions of recent work on raised interosseous venous pressure and avascular necrosis of the femoral head.

Candidate's Revision (To follow first paragraph, p 34):

Corticosteroid-induced hypercoagulability of the blood in association with fat emboli and vasculitis may additionally cause vascular sludging similar to that seen in sickle cell disease (Cosgriff et al 1950, Heimann and Freiberger 1960, Boksenbaum and Mendelson 1963).

Alcohol and corticosteroids could also cause ANFH by interfering with the femoral head vascular supply through extrinsic mechanisms. The perfusion pressure in the terminal arterial arcades decreases progressively in their smaller loops (Brookes 1964), rendering these vessels vulnerable to outside pressure (Wang et al 1977) (Revision Section 4.4.1). An increase in pressure in the bone surrounding these vessels will cause a proportional fall in their blood flow (Michelsen 1967). Nixon (1984) refers to this as a "compartment syndrome of bone." Wang et al (1977) created an animal model to explain this bone pressure increase: they found that systemic administration of corticosteroids to rabbits results in a significant and reproducible increase in marrow lipocyte volume. These

authors postulated that this increased fat cell volume could be accommodated only at the expense of other elements in the bone marrow. The low-pressure venules are probably more-susceptible to external pressure than the arterioles (Wang et al 1984); venular occlusion will result in underperfusion and secondary arteriolar insufficiency (Jones and Hungerford 1984).

There is clinical support in humans for this theory; Hungerford (1975) showed an increase in femoral head pressure (with delayed dye clearance on intramedullary venography) in patients with early ANFH associated with corticosteroid and alcohol use. Others have confirmed this finding (Solomon 1979, Wang et al 1981, Conklin et al 1984). This is not, however the complete explanation of alcohol- and corticosteroid-induced ANFH: numerous animal models of venous congestion in bone have uniformly failed to progress to bone destruction and joint deformity (Jones and Hungerford 1984). It is likely therefore that ANFH occurs as a result of a combination of these proposed vasculitic, embolic and compressive mechanisms (Jones and Hungerford 1984, Wang et al 1984).

SECTION 4.7.3 (p 39 - 40): HYPERLIPIDAEMIC ARTHROPATHIES

<u>Examiner's Comment:</u>

It was disappointing to find ....the candidate's ignoring of earlier descriptions of migrating tenosynovitis in association with hyperlipidaemia.

<u>Candidate's Revision:</u>

Helland- Hansen (1956) noted that 11 of 125 patients

with "hereditary xanthomatosis" studied by him had tendo achilles tenosynovitis - a prevalence twice as high as expected in the region of his study. Harlan et al (1966) in a large review of American patients with familial hypercholesterolaemia noted recurrent pain and swelling in the achilles tendons of two subjects. However it was left to Glueck et al (1968) to draw attention to this aspect of musculoskeletal involvement in Type II hyperlipidaemia: they described 14 patients with familial Type II hyperlipidaemia who suffered attacks of tendinitis, lasting two or three days at a time and recurring every one to three months. Sometimes these attacks were accompanied by arthritis of the first metatarsophalangeal joints or knees. The achilles tendons were most-frequently involved and in "many" patients recurrent tendinitis preceded other hyperlipidaemic manifestations (arcus, tendon xanthomata, xanthelasma and tuberous xanthomata) by years.

SECTION 6.5.6 (p 66): OTHER ALCOHOL SCREENING TESTS

Examiner's Comment:

Among the biochemical markers for alcohol, p66, one could have included the serum albumin abnormality observed by Professor Carl Bertil Laurell, which might have been of interest to validate in the study.

Candidate's Comment:

Hallen and Laurell (1972) studied a variety of plasma proteins in 40 subjects with "liver cirrhosis in a quiescent state."

Prealbumin levels were frequently subnormal. The authors felt this protein to be the most-sensitive of several plasma proteins as an indicator of impaired liver function. Prealbumin was decreased in cirrhotic patients irrespective of whether or not alcohol abuse had caused cirrhosis; low prealbumin is thus a marker of cirrhosis rather than alcohol abuse.

SECTION 7 (p 70 - 74): EPIDEMIOLOGICAL METHODS RELEVANT TO STUDIES OF ARTHRITIC POPULATIONS

Examiners' Comments: First Examiner:

The thesis includes an interesting section (p 70-74) on the pitfalls inherent in case-control investigations such as this. In this work the author has been at great pains to exclude selection bias, sample bias and information bias.

Second Examiner:

Chapter 7 is devoted to epidemiological methods relevant to studies of arthritic populations. Here the candidate discusses several sources of bias but the candidate does not show that he is thoroughly conversant with this area of research methodology, and there is no review of the considerable rheumatological literature concerning the epidemiology of rheumatic disease.

Candidate's Comment:

I cannot reconcile the comments of the two Examiners about this section of the thesis. The title of this chapter carries a

high degree of specificity - I made no attempt to review the entire epidemiological and rheumatological literature concerning the epidemiology of rheumatic disease because I felt it could not be accommodated without making the text even more "long-winded" (Examiner's words). Nevertheless, to indicate my familiarity with the rheumatological literature concerning the epidemiology of rheumatic disease I have included in their appropriate sections numerous references to work in this field by Acheson et al (1973, 1975, 1979, 1982), Fowler et al (1970), Daniellson (1964), Gold and Cangemi (1979), Kellgren et al (1952, 1958, 1961, 1963, 1964), Lawrence (1955, 1969, 1975, 1977), Peyron (1979), Solomon et al (1975, 1982), Wood and Badley (1980) and others. These references are to be found on page 267 et seq. of the main thesis.

SECTION 8 (pp 75 - 80): PSYCHOLOGICAL ASPECTS OF RHEUMATOID ARTHRITIS

Examiner's Comments:

The chapter on psychological aspects of rheumatoid arthritis is also rather scanty.

Candidate's Revision (To complete Section 8.1, p77):

It must be debatable whether studies subsequent to the review of psychological aspects of rheumatic disease by Baum (1982) have added much to understanding of the psychological changes which occur in patients with rheumatoid arthritis. Liang et al (1984) compared 76 patients with SLE and 23 with RA by their responses to the MMPI [Minnesota Multiphasic Personality Inventory, a standard instrument for measuring

psychological variables designed by Hathaway and McKinley (1943)]. Both groups of patients had significantly-elevated scores on the MMPI scales for Hypochondriasis, Depression and Hysteria irrespective of their disease duration. The authors felt that these findings indicated that Depression and Hypochondriasis are closely-related and are both also related to changes in social activity. This study was, however, heavily-flawed: only 20% of RA and 14% of SLE subjects approached by the authors agreed to take part, introducing (by their admission) a considerable element of sample bias. More-seriously, Smythe (1984) has pointed out that the Hypochondriasis, Depression and Hysteria scales of the MMPI have many pain and disability-related questions; subjects admitting to suffering pain will thus inevitably have high scores on all these scales. The MMPI is thus not an appropriate measure of the psychological state of patients with organic disease causing pain and disability (Smythe 1984). Equally, I believe that the rigidly-structured MMPI cannot recognize major psychological components which affect the clinical course and outcome of patients with RA.

Other studies of the psychological state of RA patients have yielded results which are easier to interpret. Rimon and Laakso (1984) assessed the prevalence over long periods of psychopathology in such patients; 46% of 74 women with classical or definite RA studied over a 15 year period had "psychiatric disturbances necessitating treatment" during the period of study. 41% had psychopathology at the time of study (just under half of whom were "depressive"). Only one patient had a psychotic disorder. This study was not controlled, nor did it mention the effect of treatment in the psychopathology study group. The authors however commented that psychopathology reduced the effect of antiarthritic therapy in RA patients.

The sexual problems of RA patients have until recently received scant attention.Elst et al (1984) found that RA sufferers (but not patients with ankylosing spondylitis) tended to avoid sex when compared with controls. In women, the level of sexual aversion related weakly to disease variables such as joint index and erythrocyte sedimentation rate. Yoshino and Orchida (1981) studied sexual problems in Japanese women with RA. Their uncontrolled study similarly showed a decline in sexual desire in their subjects (whose spouses also suffered diminished libido).

It is interesting to speculate whether this sexual aversion and the alcohol aversion that I noted in my RA subjects in Study A are part of the same phenomenon. As in the case of alcohol aversion, RA patients who avoid sexual activity probably do so for a variety of reasons but I believe that common to both is the feeling that "life with a chronic painful disease allows little room for pleasures." Possibly this attitude contributes to the depression felt by so many RA patients.

SECTION 10.2.2 (p 91 - 92): SUBJECTS WITH RHEUMATOID ARTHRITIS

Examiner's Comments:

I would perhaps have liked more clinical data regarding the RA patients.

Candidate's Comment:

I presume the examiner refers to information about predominant joint involvement, associated medical conditions and drug therapy. Unfortunately this information was not tabulated for study.

SECTION 10.4 (p 96 - 97): VENESECTION AND BLOOD PRESSURE

Examiner's Comment:

The samples were taken at 9.00 am and non-fasting. It would have been advantageous to take samples fasting before breakfast, and in any case the reasons (practical?) for the chosen routine could have been stated.

Candidate's Comment:

I agree that fasting samples would have been ideal but unfortunately this was not practical; subjects were routinely venesected by phlebotomists after breakfast, the decision about which tests to undertake often being made just before phlebotomy. Fasting samples would have meant double venesection with an increased likelihood of non-compliance by subjects and their medical attendants (most patients belonged to consultants with whom I had only casual links). The examiner is thus correct in surmising that the non-fasting routine was chosen for pragmatic reasons.

SECTION 11.3 (p 107 - 108): ALCOHOL CONSUMPTION SCORES

Examiner's Comment:

On page 108 it is stated that consumption before the age

of 30 was disregarded as bearing "no relation to later consumption". How sure can one be that this is so?

Candidate's Comment:

I could not be sure, but many subjects told me that they drank "much more when younger." Closer questioning revealed that those who drank heavily in their "youth" but became abstemious later, cut their consumption in their mid-20's coincident with marriage and promotion at work. I therefore chose the age of 30 as an arbitrary cut-off point for "mature adult" alcohol consumption as most subjects had settled into long-term lifestyle patterns by that age.

SECTION 11.8.1 (p 117): INTRA-OBSERVER RELIABILITY

Examiner's Comment:

A reference for Kendall's tau test would have been indicated.

Candidate's Comment:

The appropriate reference is: Kendall MG. Rank Correlation Methods. London, Griffin, 4th Ed 1970.

SECTION 11.10 (p 121): BLOOD PRESSURE AND REPORTED CURRENT ALCOHOL CONSUMPTION

Examiner's Comment:

On page 121 the lack of correlation between current QF score and blood pressure is shown. What about the relation with earlier QF scores?

Candidate's Comment:

There was a similar lack of correlation between earlier QF scores and blood pressure.

SECTION 12.2 (p 127): CORRELATION BETWEEN CLINICAL, HISTOLOGICAL AND PLAIN RADIOLOGICAL FINDINGS

Examiner's Comment:

The patient's complaints were from the left hip but the only abnormality was at the right hip. The correct side is probably the left.

Candidate's Comment:

The Examiner is correct. Symptoms, signs and radiological abnormalities were all confined to the left side.

SECTION 14.1.5 (p 145 - 146): QF QUESTIONNAIRE VALIDATION

Examiner's Comment:

The reliability of any interview method regarding alcohol consumption can be questioned. One way of validation that was not used would have been spouse interviews, another the check for records of arrests for drunken driving and other alcohol-related offences. Although I fully accept the probably-insurmountable problems involved in such approaches, they could have been discussed.

Candidate's Comment:

Spouse interviews would have been extremely valuable in corroborating subjects' answers and would have been acceptable in these studies if the spouse had been available for interview; unfortunately this was very rarely the case.Court records were unavailable and anyway would have indicated "problem drinking" behaviour rather than "abnormal drinking" which was under investigation in Study A. In Study C the CAGE questionnaire served the purpose of assessing "problem drinking" and of corroborating QF alcohol consumption scores.

Several individuals (notably Dr Joan Trowell of the Liver Unit, John Radcliffe Hospital, Oxford) felt that Studies A and C would have been strengthened by the inclusion of a blood alcohol estimation performed simultaneously with the GGT, SUA and MCV. Dr Trowell commented that this would have allowed easier detection of female alcohol abusers, who are especially-reluctant to admit their alcohol consumption. I agree; if I were to repeat these studies I would assay blood alcohol. My concern at the time was about the lack of security of blood alcohol results, which

might have had legal implications (for example the incidental discovery of elevated blood alcohol levels in fit individuals who had driven themselves to hospital for elective surgery). Clearly this is not a consideration in ill patients admitted to medical wards.

SECTION 14.2 (p 146 - 147): SELECTION OF SUBJECTS (PARTICULARLY CONTROLS) FOR THE STUDY

Examiner's Comments:

The selection of normal controls seems odd, when there must surely have been access to other subjects in the Oxford health region.

Candidate's Comment:

The answer to this important question is detailed at length in Section 14.2

SECTION 14.4 (p148 - 150): QF SCORES:

Examiner's Comment:

It was a little surprising to see no discussion about life-time alcohol consumption patterns in OA vs RA in terms of preceding psychological and genetic factors in RA patients.

Candidate's Comments:

My study shows that premorbid heavy alcohol consumption is more-common amongst OA patients than amongst RA patients and control subjects. Little is known of the premorbid personality in RA patients; Baker and Brewerton (1981) suggested that people who go on to develop RA might have certain personality traits reflected in an unusually-increased prevalence of "life events" in their pre-RA existence; I suppose it must be conceivable that such traits might be associated with lifelong abstemiousness. However other workers (Section 8.1, p77) have not confirmed differences between the premorbid personality of RA patients and controls.

Little is known also of genetic or familial factors determining alcohol consumption. Family, adoption and twin studies have not resolved whether there is a genetically- transmitted predisposition to the development of alcoholism (Goodwin 1979); "alcoholism" (or "problem drinking") is however not HLA- linked (Robertson et al 1984). It thus remains conceivable that a genetic susceptibility to RA is linked with genetic resistance to alcoholism.

SECTION 16.7 (p 181 - 182): QUESTIONNAIRE

Examiner's Comments:

On page 182 it is implied that gout is diagnosed by elevated SUA levels, which is of course not possible if no typical symptoms are observed and crystal findings are made. Furthermore, the influence of drugs on SUA would be likely to enter a bias between the groups, RA

patients probably using more of the uricosuric NSAID's.

Candidate's Comment:

I stated the diagnostic criteria for gout in these studies in Section 12.3 (pp 128 - 129) and in Section 17.9 (p 193). Subjects had gout if they gave a history of recurrent attacks of painful swelling and redness of one or other of the first metatarsophalangeal joint, never lasting longer than a fortnight, with complete remission between attacks. Similar attacks at joints other than the first metatarsophalangeal, together with past or present evidence of elevated SUA (above 400 micromol/litre in males and 350 micromol/litre in females) were considered to indicate gout. In Study B, I had no way of establishing past SUA levels so subjects with attacks at joints other than the first metatarsophalangeal were deemed to have "possible" gout. It can thus be seen that SUA levels played a lesser role than clinical presentation in deciding whether or not subjects had suffered gout.

The examiner's second point about NSAI drugs entering a potential bias between diagnostic groups is acknowledged in the paragraph 4 (Drugs Decreasing SUA) in Section 15.4.1 on page 166.

SECTION 17.12 (p 195): DECREASED RANGE OF JOINT MOVEMENT:

Examiner's Comments:

The candidate gives no indication of how limited joint mobility was measured and in the absence of a normal population no

definition of range of motion is possible and the conclusion that joint hypomobility is increased in this alcoholic population is open to question.

<u>Candidate's Comment:</u>

The examiner is correct in pointing out the omission of the method of assessment of joint hypomobility. I used the method of Raskin and Lawless (1982); they stated that "decreased... range of motion [secondary to trauma] was defined by ....abnormality of at least 10 degrees as compared to standard articular charts (McCarty 1979) and as compared to the contralateral joint." I agree also that without a control population the conclusion that joint hypomobility is increased in this alcoholic population is open to question; I emphasised this along with conclusions about other aspects of the study in Section 22.3. however the Examiner later states that I have used Beighton's Scoring System for hypermobility and drawn inferences from low scores about joint hypomobility in alcoholics. I must refute this: any conclusions I drew from mobility scores related only to hypermobility.

I agree with the Examiner that "it is not acceptable to draw comparisons [as in section 18.10] between joint hypomobility prevalence in the alcoholics (older) and in medical students (young) because mobility scores decrease with age." Apart from this error on my part, my conclusions about joint hypomobility relate only to the distribution of joints with abnormally-diminished movement and to the causes of this diminution in movement.

<u>OTHER COMMENTS:</u>

Examiner's Comment:

There is no information about the alcohol consumption patterns in the Oxford Region. The fact that more OA men were heavier drinkers than RA stands as it is but there is nowhere any indication of how this pattern relates to the community.

Candidate's Comment:

The Examiner is correct. There was (at the time of submission of the thesis) no information about community patterns of alcohol consumption in the Oxford Region. The figures for England and Wales as a whole do not serve for comparison because they are aggregate figures which do not reflect differences in local consumption.

Examiner's Comment:

It is difficult to accept the impossibility of finding a control population [in Study B, Sections 16 to 18]. Why not use random age- and sex- matched healthy individuals?

Candidate's Comment:

In retrospect I agree with the Examiner. A control group such as he suggests would at least have allowed assessment of the significance of interesting findings such as the apparently-frequent meniscal problems in alcoholics. At the time I planned the study I felt that the difficulty in finding a suitable control group would result inevitably in an unsuitable choice of controls, open to considerable

criticism, which would detract from other aspects of the study.

Examiner's Comment:

Figure 20.9.2 does not show a linear relationship between GGT and QF score as implied by the regression line.

Candidate's Comment:

This was also my initial impression. The linear regression line however gave the "best fit" in terms of statistical significance - there were no significant relationships between these variables when tested by logarithmic and exponential regressions.

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