

the demonstration with rapid frozen sections and projected slides. In appropriate cases it is worthwhile too for the other laboratory consultants to attend and take part in what is really the best form of clinicopathological conference—spontaneous discussion by clinicians and pathologists in the context of the story of the case as it unfolds in the post-mortem room.

Paradoxically the coroner system is in part responsible for the deterioration in standards of the post-mortem services. Designed originally as an insurance against unnatural deaths going uninvestigated, it has had grafted on to it the investigation of countless thousands of perfectly natural deaths occurring without any suspicion of foul play. Most of the necropsies arising from this work fall to the lot of already overworked hospital pathologists, who are thereby condemned to neglect more important hospital duties to carry out large numbers of these hack operations. It has been widely recognized that some reform is long overdue, and as far back as 1965 an interdepartmental committee (the Broderick committee) was set up to inquire into death certification and the working of the coroner system. The report of this committee has been expected almost monthly for some two years now, and meanwhile the existence of the committee is being used as an excuse to make no change in existing arrangements.

Where, it is natural to ask, does the Royal College of Pathologists stand in this unsatisfactory state of affairs? Improvement of standards and the testing of proficiency by appropriate examinations were matters foremost in the minds of those active in the founding of the college in 1962. Candidates at the final membership examination in morbid anatomy and histopathology are given a searching test of their knowledge of post-mortem work and are usually (but not always) required to carry out a necropsy under highly critical eyes. The fruits of this system are improving standards of technique and demonstration. But it will be tragic if consultant morbid anatomists are prevented by defects in organization from bringing back to the post-mortem room its vital role in undergraduate, postgraduate, and continuing medical education.

The Arthropathy of Haemochromatosis

Since the whole body is perfused with fluid supersaturated in bone mineral¹ it is amazing that apatite crystals normally form only in bones and teeth. What stops the rest of the body from becoming "furred up"?

It has been suggested that an inhibitory substance, pyrophosphate, acts as a "water softener," for it retards both the growth and the dissolution of apatite crystals *in vitro*.² Diphosphonates, chemically related to pyrophosphate and more resistant to hydrolysis,³ have been shown to inhibit vitamin-D-induced calcification in rats⁴ and in the same species also to inhibit osteoporosis due to immobilization.⁵ Similar research may in the end provide a solution to the problems of the abnormal calcification of soft tissue. Subcutaneous calcification in dermatomyositis and scleroderma, calcification of the arterial walls in diabetes, and the widespread calcification in renal failure all await elucidation.

Pyrophosphate may also function as a substrate for the enzyme alkaline phosphatase,⁶ and this would explain the raised levels of urinary pyrophosphate and the bony dis-

solution seen in hypophosphatasia.⁶ It might also explain the increased deposition of pyrophosphate in the tissues described recently in a case of hypophosphatasia.⁷

In patients with pyrophosphate arthropathy the levels of serum alkaline phosphatase have been normal,⁸ as have levels of serum and urinary pyrophosphate.⁹ But in these patients' synovial fluid the concentration of pyrophosphate is higher and the concentration of alkaline phosphatase is lower than in controls.⁹ This suggests there might be a local disturbance of pyrophosphate metabolism within the joints. The sequence of crystal formation in this disease is not clearly understood. The crystals may be formed in cartilage and only later discharged into the surrounding synovial fluid.

Calcification in cartilage has been described in association with gout,¹⁰ rheumatoid arthritis,¹¹ joint trauma,¹² osteoarthritis,¹³ and senescence.¹³ In addition cases have occurred in metabolic diseases such as ochronosis,¹⁴ hyperparathyroidism,¹⁵ diabetes,¹⁶ and haemochromatosis.¹⁷ Whether these deposits are a part of the primary disorder has not been established.

I. W. Dymock and colleagues¹⁸ recently reviewed 63 cases of haemochromatosis, 35 of which had radiological or clinical evidence of arthropathy and 16 had chondrocalcinosis. There was no relationship between the onset of haemochromatosis and the onset of arthropathy. But age of onset of haemochromatosis did seem to be the determining factor in the development of arthropathy, there being an increase in the incidence of arthropathy in those patients developing haemochromatosis after their 50th birthday. Treatment by venesection did not influence the arthropathy. Clinically the first change was a progressive stiffness in the second and third metacarpophalangeal joints with bony enlargement and increasing limitation of movement sometimes resembling rheumatoid arthritis. However, ulnar deviation was not observed, and the radiological appearance differed from that of rheumatoid arthritis in that there was radiological juxta-articular sclerosis rather than osteoporosis, and marginal erosions were uncommon.

In some patients a more generalized pattern was seen. The large joints were affected, with arthritis at the hips and knees and chronic radiological change indistinguishable from osteoarthritis. Cartilage became calcified in knees, hips, symphysis pubis, tendo Achillis, and plantar fascia. In the spine calcification occurred in the lateral margins of the intervertebral discs rather than the lateral ligaments of the spine. In addition to the chronic progressive joint disease 12 patients experienced acute inflammatory attacks, usually of the knees, lasting a few days to a few weeks and clearing with phenylbutazone or indomethacin and joint aspiration.

The aetiology of the arthropathy of haemochromatosis is unknown, but deposits of haemosiderin have been found in the synovium and articular cartilage of patients with haemochromatosis. If pyrophosphate activity is inhibited by metal ions such as Fe⁺⁺ as suggested by D. J. McCarty and colleagues,¹⁹ that might explain the precipitation of pyrophosphate in this disease.

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Sniffing Syndrome

The inhalation of vapours such as anaesthetic agents for their pleasurable effects has been recognized for many years, but the practice spread in the 1950s with the use of petrol fumes as intoxicants,¹ to be followed in the next decade by "glue sniffing".² A variety of products have subsequently been sniffed in the quest for pleasure and elation, the most popular being solvents, cleaners, paints, thinners, lacquers, and recently pressurized aerosols.

Glue sniffing, rarely reported in Great Britain,^{3,4} has been the most popular sniffing syndrome in America. The practice has caused serious cerebral damage, aplastic anaemia, and even death from asphyxiation by a plastic bag used for inhalation.⁵ Recently E. T. O'Brien and his colleagues⁶ reported a case showing that there are serious dangers in the sniffing pastime. Acute hepatic and renal damage developed in a 19-year-old glue sniffer after inhalation of vapour from a cleaner, the main constituent of which was toluene. This toxic chemical is present in the vapours of most glues and is probably responsible for the pleasurable effects. It was found in high concentration in the patient's blood and was almost certainly the cause of the toxic symptoms.

Other varieties of the sniffing syndrome may be equally dangerous. The inhalation of petrol fumes has caused severe hepatic damage and lead encephalopathy.⁵ Sniffing of a popular spot remover containing trichlorethylene has resulted in acute renal tubular necrosis and acute hepatic necrosis.⁷ Possibly the most dangerous practice is the inhalation of fluorinated hydrocarbons from aerosol containers. A recent review⁸ reported 110 cases of sudden death during the last decade in American teenage sniffers. These sudden deaths from sniffing differed from previously reported fatalities due to asphyxiation by a plastic bag in that death was usually preceded by a period of hyperactivity or emotional stress. At necropsy no physical abnormalities were found. Deaths followed the sniffing of vapours of glue, solvents, and petrol, but the largest number occurred after inhalation of aerosols in which the fluorinated hydrocarbons act as agents for propelling ingredients out of the can. Severe cardiac arrhythmias, intensified by hypercapnia, stress, or activity, were considered the most likely explanation for sudden death.

The "inert" propellant gases from pressurized nebulizers, which are also fluorinated hydrocarbons, have been shown to sensitize the hearts of mice to asphyxia-induced sinus bradycardia, atrioventricular block, and ventricular T-wave depression.⁹ Sensitization is rapid in onset, long-lasting, and potentially lethal. The question has been raised whether sudden death in young people who inhale aerosols and in asthmatics using pressurized nebulizers could be due to a similar cardiotoxic effect, with perhaps sensitization of the heart to endogenous catecholamines, the release of

which may be enhanced by such factors as hypoxia and hypercapnia. Moreover, fluorinated hydrocarbons have recently been found in the blood of volunteers using nebulizers.¹⁰ These findings may not only have a bearing on the sudden death of some asthmatics but also raise questions about the effect on persons with asthma and cardiac disease of aerosol dispensers used for cosmetic, household, and other purposes.

Diagnosis of a sniffing syndrome can be difficult, and, as O'Brien and his colleagues stress, there may be no clinical abnormality when the patient is first seen. The differential diagnosis includes alcoholic intoxication, cerebral disease, gastroenteritis, infectious hepatitis, renal failure, and various psychiatric disturbances, and the syndrome should be considered in any obscure and unexplained illness in teenagers. The characteristic smell of solvent or glue may be present, and the laboratory can be of assistance in isolating the toxic substance from breath or blood, and, with toluene, in the detection of hippuric acid in the urine.

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Genitourinary Tuberculosis

In contrast to the steady decline in numbers of new cases of tuberculosis of the lung, genitourinary tuberculosis shows little evidence of any falling-off,¹ nor are new cases specially prevalent in immigrants from overseas. On the contrary, it seems to be something that the British migrant takes with him to Australia.²

There is no ready method of screening the population for genitourinary tuberculosis like mass radiography of the chest, and effective detection and treatment of the disease depend on the diligent investigation of its early symptoms. These may be slight. The earliest lesion of genitourinary tuberculosis is likely to be a small tuberculous focus in a renal papilla. It will be silent until it ruptures into the renal pelvis and discharges its more or less irritating contents into the urine. At this stage the patient may have irritation of the bladder, frequency, and discomfort on voiding, and cystoscopy may show some inflammation round a ureteric orifice and even some minute tubercles. But often the symptoms are mistaken for those of bacterial cystitis or of a common condition which mimics cystitis but seems to have no bacteriologically identifiable cause. The patient will usually have many polymorphs in the spun deposit of the urine, and the urine will be acid and sterile on ordinary culture. The finding of an acid pyuria should call for the special culture of six early morning specimens of urine for *Mycobacterium tuberculosis*.

At a later stage haematuria may be the symptom which brings the patient to the doctor, and since every case of haematuria should be fully investigated by excretion pyelography and cystoscopy few cases of tuberculosis with this symptom will be missed. Less often it is ureteric colic without obvious haematuria which troubles the patient. In some