HAEMOSIDEROSIS AND HAEMOCHROMATOSIS OF SYNOVIAL TISSUES

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Rusty pigmentation of the synovial lining is occasionally seen in joints opened at operation or at autopsy. Joints with a large synovial surface, such as the knee joint, may present a striking picture when the pigmentation is intense. In smaller joints and with lesser degrees of pigmentation the phenomenon may escape detection, and statistics relating to the condition cannot be obtained. In its grosser manifestations the condition is a rare one. The rusty discolouration is always the result of an accumulation of haematogenous pigment, principally haemosiderin, in the stratum synoviale. It has two causes. The first, and commoner, is the absorption of blood shed into the joint cavity (haemarthrosis). The second and little known cause is haemochromatosis, a systemic disease in which the joints participate only incidentally, but regularly.

HAEMARTHROSIS AS A CAUSE OF SYNOVIAL PIGMENTATION

Most traumatic effusions are watery, with only a little bleeding into the joint. Severe injuries, such as fracture of the intracapsular portions of bones, generally cause much bleeding; large effusions of blood may follow trivial injuries in sufferers from one of the haemorrhagic diseases and in patients with intra-articular tumours. Even when consisting mainly of blood with little dilution by watery exudate, the aspirated fluid from a haemarthrosis usually contains no clot and fails to clot in vitro. Seeliger (1926), however, showed that neither synovial cells nor synovial fluids possess any anticoagulant property, and by injecting blood into rabbits’ joints he demonstrated that clotting does occur rapidly but that the blood soon becomes fluid again. This he attributed to joint movement, which breaks up the clot and debrinates the blood. While fragments of blood-clot may be found on laying open a joint after a haemorrhage, it is certainly the rule that a bloody joint effusion is fluid and apparently debrinated. In course of time lysis of the red cells occurs and degradation of haemoglobin proceeds as in any haemotoma. A positive van den Bergh reaction for bilirubin in the joint fluid may be obtained a long time after the haemorrhage. The iron-containing particulate pigment, haemosiderin, is taken up by the phagocytic synovial-lining cells. Micro-sections stained by the Prussian blue reagents show clusters of fine, iron-reacting particles in these cells and also large aggregates in macrophages in the looser tissues of the stratum synoviale beneath the synovial surface (Fig. 1). There it endures for an indefinite period of time. Occasionally, after a recent haemorrhage, bright yellow crystals of haematoidin, not giving the iron reaction, may be seen; but it is the haemosiderin, itself a golden yellow pigment, that is mainly responsible for the gross pigmentation of the synovial tissues (Fig. 2). The condition is therefore correctly described by the term synovial siderosis or haemosiderosis.

It is doubtful whether the amount of haemosiderin absorbed from a single intra-articular haemorrhage is sufficient to cause a noticeable gross discolouration of the synovial lining. In every instance of pronounced rusty pigmentation in my experience there has been direct or presumptive evidence of repeated haemarthrosis, as in haemophilia and in synovial haemangioma, or of long-continued oozing of blood, as from the vascular granulation tissue of a chronic rheumatoid arthritic joint or as in villo-nodular synovitis, a condition whose nosological placing is still debatable.
Haemophilia is an important cause of synovial siderosis because repeated intra-articular haemorrhages occur so frequently in this disease. Thomas (1936) records a 78 per cent incidence of joint involvement in his series of ninety-eight haemophiliacs, permanent joint deformity being present in 61 per cent. Intermittent haemarthroses alone do not quickly lead to the disorganised and disabled joint of haemophilic arthritis. Continued distension of the joint with blood, long-standing mechanical interference with movement, and haemorrhages into the bone ends and beneath the cartilages seem to be some of the factors concerned. But intermittent haemarthroses lead to synovial siderosis which increases in degree after every haemorrhage. I have found in a haemophiliac at post-mortem examination some joints whose

![Fig. 1](image1.png) ![Fig. 2](image2.png)

**Fig. 1** Siderosis of synovial membrane in chronic haemarthrosis. Figure 1—Prussian blue reaction shows a fine peppering of haemosiderin in the synovial lining and coarser aggregates of the pigment in macrophages beneath the surface. Synovial haemangioma (not shown in this section) was the cause of the repeated intra-articular bleedings. (Section stained with potassium-ferrocyanide, hydrochloric acid and carmalum, ×50.) **Fig. 2**—From the same joint as Figure 1, but in this section—not treated with the Prussian blue reagents—the natural golden yellow colour of the haemosiderin with transmitted light is shown. Note the heavy load of pigment in the macrophages in the loose tissues of stratum synoviale below the surface. (Haematoxylin and eosin, ×176.)

only abnormality was a vivid rusty staining of synovial membrane, while other joints showed advanced disorganisation and radiographic appearances typical of well developed haemophilic arthritis. In these latter joints sections show the synovial tissues to be very heavily laden with haemosiderin, although to the naked eye the rusty colour is usually obscured by the dark red organising thrombus that fills what is left of the joint cavity. In the siderotic but otherwise intact joints haemosiderin is confined to the synovial lining cells and to the tissues immediately below. The gross and microscopical appearances of these joints of the haemophiliac are in no way different from those seen in joints into which repeated bleedings have occurred from some other cause.

**SYNOVIAL PIGMENTATION IN HAEMOCHROMATOSIS**

Sheldon (1935), in an exhaustive review of the literature for his monograph in which he collected the records of 311 cases of haemochromatosis, found only twelve references to the joints, which seem to have been examined in only fifteen instances of the disease. In all but one case (Gaskell et al. 1914), in which the only information given is "joints—natural," a dark reddish-brown or rusty pigmentation of the synovial membrane was recorded. Sheldon
adds another case of his own and reproduces a photomicrograph showing haemosiderin in the synovial lining, and I have briefly alluded to the phenomenon elsewhere (Collins 1949). That many joints may be simultaneously pigmented in haemochromatosis is shown by such records as those of my Case 4, and of Schubert and Geipel (1921) who described intense pigmentation of the synovial membrane in the knee, hip, shoulder and elbow joints.

The records of four hitherto unreported cases of haemochromatosis coming to autopsy in Leeds and in which joints were examined may be given in brief.

![Image](image_url)

**FIG. 3**

Haemochromatosis of synovial membrane. From knee joint of haemochromatosis Case 1. Haemosiderin giving a strong Prussian blue reaction is virtually confined to the lining layer of synovial cells. (Section stained with potassium-ferrocyanide, hydrochloric acid and haematoxylin and eosin. - 180.)

**CASE REPORTS**

**Case 1**—A man aged sixty-four years. Bronzing of skin for twelve months, diabetic symptoms for two months before death. *Post-mortem examination*—Widespread haemochromatosis of viscera was seen, with fibrosis of liver and pancreas. *Joints*—Hip and knee joints on the right side both showed rusty pigmentation of synovial membrane, more developed in the knee joint. Microscopically a finely granular but heavy deposit of haemosiderin is seen within the cells lining the joint cavity. Hardly any pigment is seen below the surface (Fig. 3).

**Case 2**—A woman aged forty-two years. Liver cirrhosis and macrocytic anaemia had been diagnosed three and a half years before death. Frank diabetes developed later. Skin pigmentation appeared later still, and the correct diagnosis was made only shortly before death from rupture of oesophageal varices. *Post-mortem examination*—Obvious haemochromatosis of most viscera, atrophic cirrhosis of liver. *Joints*—Hip and knee joints on the right side were examined. The synovial membrane of the hip joint was of a rusty colour and sections showed much pigment in the lining layer of synovial cells. The knee joint appeared normal to the naked eye; no sections were made.

**Case 3**—A man aged sixty-five years, admitted with carcinoma of larynx. Haemochromatosis was not suspected. *Post-mortem examination*—There was primary carcinoma of larynx, generalised haemochromatosis, and cirrhosis of liver with primary malignant liver-cell carcinoma. *Joints*—Deep siderotic staining of the synovial lining of both knee joints was to be seen.

**Case 4**—A man aged sixty-five years, admitted with perinephric abscess. Haemochromatosis was not suspected. *Post-mortem examination*—There was haemochromatosis grossly affecting liver,
pancreas and coeliac lymph glands. Liver cirrhosis. The microscope revealed pigment deposition in many other organs and tissues. Joints—Both knee joints and both shoulder joints were opened and all showed an intense rusty brown pigmentation of the synovial lining, sometimes patchy in distribution. Various samples of the pigmented tissue gave a strong Prussian blue reaction in the gross specimen (Fig. 4). Microscopically, fine particles of haemosiderin lie in profusion in the cells upon and immediately beneath the synovial surface. Aggregates of small particles and larger granules lie in small groups of histiocytes immediately beneath the synovial lining, and a cut of pigment is sometimes seen in the walls of capillaries or very small arterioles. The deeper tissues of stratum synoviale and stratum fibrosum contain no pigment at all.

![Image](haemochromatosis.jpg)

**Fig. 4**

Haemochromatosis of synovial membrane. Knee joint from haemochromatosis Case 4. The rusty pigmentation of the synovial tissues is well seen on the front and sides of the lower end of the femur. The patella has been removed. The deep blue tissue mass (left) is the anterior fat pad from the same joint. Its synovial covering was heavily pigmented and the tissue has been exposed to potassium-ferrocyanide and hydrochloric acid resulting in this vivid Prussian blue reaction.

### DISCUSSION

The absence of pigment in the deeper parts of the synovial membrane in haemochromatosis has previously been remarked upon by Frisch (1922). It is a feature which seems to distinguish haemochromatosis from synovial siderosis after haemarthrosis, because in this the pigment often lies in macrophages at some distance below the synovial surface. The distinction is apparent when Figures 1 and 3 are compared. In generalised haemochromatosis the pigment at some time circulates in the body and is removed from the circulation by the phagocytic synovial-lining cells which, in the words of Policard (1936), constitute the articular territory of the reticulo-endothelial system. Histiocytes and reticulo-endothelial cells of mesenchymal origin are not, however, the only cells which assimilate pigment in generalised haemochromatosis; much pigment is also commonly seen in parenchymatous cells of the liver, in epithelial cells of pancreas, stomach, thyroid, salivary glands and many other glandular organs, in smooth muscle and, as Bork (1928) especially emphasized, in the media and adventitia of the arteries in many viscera. Pigmentation of vessel walls was seen in the joint tissues in Case 4. Sheldon also refers to pigmentation of cartilage in various parts of the body, including the joints, but I have not encountered any discolouration of the articular cartilages, and this change seems to be less constant than the synovial pigmentation.
Haemosiderin is not the only pigment that appears in the tissues in haemochromatosis. An almost black, crystalline pigment, haemofuscin, is also found. Haemofuscin contains no iron, but it does contain sulphur and is thought to be related to the pigment melanin, which is itself mainly responsible for the discolouration of the skin. In my studies of the joints in haemochromatosis I was able to identify only haemosiderin in the synovial tissues. The cause and precise nature of the disturbed pigment metabolism in haemochromatosis are as yet unknown. Theories need not be discussed here. Attempts to reproduce the disease by injection of iron in various forms into animals have failed (Polson 1928, 1933); liver cirrhosis and pancreatic fibrosis do not follow, although the iron collects in the reticulo-endothelial, histiocytic and certain secreting glandular cells of the body. No observations on the joint tissues in experimental animals are recorded but it is probable that the histiocytes of the synovial lining would have taken up some of the iron, sincetrypan blue is absorbed by these cells from the circulation (Kuhns and Weatherford 1936). Reports have appeared in recent years, following that of Kark (1937), of haemochromatosis developing in patients who have received a great many transfusions. Such cases are not numerous; Schwartz and Blumenthal (1948) collected thirteen, and no information is available about the state of the joints. It would be interesting to know whether—as seems probable—pigmentation of synovial tissues occurs in this exogenous haemochromatosis as it does in the spontaneous disease.

Haemochromatosis is a rather rare disease; 436 cases reported in the literature were collected by Berk and Lieber (1941). The incidence is about one in a thousand autopsies at Leeds General Infirmary (Stewart 1931). It is frequently undiagnosed before death. It would be a rare but possible chance for the diagnosis to be indicated by the appearance of the synovial tissues at arthroscopy.

The question whether haemochromatosis can lead to any disabling articular disease remains to be discussed. In my view this is not the case. In each of these joints I have examined, in which there was synovial pigmentation as a part of generalised haemochromatosis, I have found no associated disease except a mild degree of osteoarthritis such as might be expected in any other patient of similar age. Dekkers (1940), however, describes a patient with rheumatoid polyarthritis and bronzed diabetes and, incidentally, points out that gold therapy was contra-indicated because of the associated liver and kidney damage. The concurrence of rheumatoid arthritis and haemochromatosis in this case was probably fortuitous.

There is no evidence that the accumulation of haemosiderin in mesenchymal phagocytes stimulates any inflammatory reaction or fibrosis. Examination of many sections of pigmented synovial tissues leads me to assume that the deposits of haemosiderin are entirely bland in their effect. The view that siderosis is not the cause of the associated liver fibrosis has been held for many years and has been confirmed by the recent observations by Herbut and Tamaki (1946) on the variable association of cirrhosis, pigmentation and diabetes, and by Wyatt et al. (1950) on transfusional siderosis. Synovial siderosis, therefore, whether resulting from absorption of blood from the joint cavity or from pigmentation of the joint tissues in generalised haemochromatosis, leads per se to no disability.

**SUMMARY**

1. Rusty staining of the synovial membrane is the gross manifestation of loading of phagocytic synovial-lining cells and of macrophages in the stratum synoviale with haemosiderin.
2. Absorption of blood effused into the joint cavities is the commonest cause of such synovial pigmentation.
3. Obvious discolouration of the synovial tissues usually follows only after repeated haemarthroses, in such conditions as haemophilia, synovial tumour and in some cases of chronic rheumatoid arthritis.
4. An identical naked-eye appearance is seen in multiple joints of patients with generalised haemochromatosis.

5. In haemochromatosis the iron-containing pigment tends to be confined to the surface layer of cells of the synovial membrane.

6. The presence of haemosiderin in synovial cells, *per se*, leads to no disability of the joint and is unaccompanied either by inflammatory reaction or fibrosis. Arthritis in a patient with haemochromatosis is fortuitous.

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REFERENCES


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