It is now recognized, as a result of absorption studies, that there is defective vitamin-B₁₂ absorption after total gastrectomy and in many instances after partial gastrectomy. It is therefore important that the vitamin should be administered intramuscularly to certain patients after these operations have been performed. Similar remarks apply to patients with ulcerative colitis and certain types of ileitis.

In view of the fact that large oral doses of vitamin B₁₂ lead to appropriate absorption in the absence of intrinsic factor it is probably sufficient to administer massive dosage of the vitamin by mouth. This could apply to the treatment of pernicious anaemia, but remains to be proved by prolonged clinical trials. In any case, it is important to realize that patients who have developed megaloblastic anaemia as a result of defective absorption will have severe depletion of their vitamin-B₁₂ stores. It is impossible to restore this to normal by intestinal absorption alone, and it is therefore important, in the first place, to give vitamin B₁₂ in relatively large doses intramuscularly.

Summary

There are now at least three highly purified preparations of intrinsic factor, with molecular weights of approximately 5,000, 15,000, and 40,000 respectively. They are apparently homogeneous and belong to the group of mucoproteins. The two with lower molecular weights have low vitamin-B₁₂-binding activity.

A substance has also been obtained which inhibits vitamin-B₁₂ absorption. The presence of such a substance or substances in intrinsic factor concentrates could explain certain inhibitory phenomena previously ascribed to species specificity. This has been borne out by the observation that human gastric juice in small quantities stimulates absorption of vitamin B₁₂ in the rat but is inhibitory in larger amounts. The last word has not yet been said in relation to the clinical use of intrinsic factor preparations by mouth, since a single dose of the inhibitory substance maintains its effect on vitamin-B₁₂ absorption for a long period.

Intrinsic-factor secretion is under the influence of the parasympathetic nervous system and possibly also the thyroid.

The intestinal absorption of vitamin B₁₂ has been shown to occur in the middle third of the small intestine in the rat but possibly in the lower ileum in human beings.

It seems that some form of binding to protein is necessary for intestinal absorption of vitamin B₁₂. This binding need not be to intrinsic factor itself. Studies of absorption with increasing dosage, as well as with analogues of the vitamin, present evidence that an enzyme mechanism is involved in its intestinal absorption.

It has recently been shown that sorbitol, a hexahydric alcohol derived from glucose, increases the absorption of vitamin B₁₂ from the intestine.

New knowledge in relation to intrinsic factor and vitamin B₁₂ has proved of use both in diagnosis and in therapy, especially in relation to treated pernicious anaemia, subacute combined degeneration, gastric resections, and intestinal disorders.

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WEBER-CHRISTIAN DISEASE WITH VISCERAL INVOLVEMENT AN EXAMPLE WITH HEPATIC ENLARGEMENT

BY

SAMUEL ORAM, M.D., F.R.C.P.

Physician, King's College Hospital, London

AND

GEORGE M. COCHRANE, M.B., B.Ch.

Senior House Officer, Dulwich Hospital, London

Although commonly known in English-speaking countries as Weber-Christian disease, a typical example of the syndrome was first published by Pfeifer (1892), and details of a second patient were described by Gilchrist and Ketron (1916). It was Brill (1936) who first referred to the condition as Weber-Christian disease, and on the Continent it is commonly known as Pfeifer-Weber-Christian disease. Weber (1925) drew attention to these two previously recorded patients in his own paper, and there is no doubt that to him must go the credit of recognizing the condition as a distinct entity. To Weber's original title "Relapsing Non-Suppurative Nodular Panniculitis" Christian (1928) added the word "febrile" to emphasize an important feature likely to arouse the interest of the clinician.

The object of recording this case in some detail is to emphasize that the disease has been too long considered as localized to the skin, whereas certain viscera and other organs may be extensively involved by the fatty metamorphosis. Such involvement may give rise to varied symptoms, including retrosternal pain, pain and swelling in joints, pain in bone, and also abdominal pain, and these symptoms may prove puzzling if the syndrome is not recognized. Rarely the visceral involvement is so extensive that it results in death.

The following case presented certain unusual features. There was severe fatty change in the liver, confirmed at laparotomy, and the only other example of such extensive hepatic involvement that we can find is that of Hanrahan *et al.* (1951). Unlike their case, which was fatal, our patient's hepatomegaly preceded the appearance of the typical skin lesions. Continuous pyrexia also preceded the rash by eleven weeks, thus rendering clinical diagnosis impossible in the early stages.

Case Report

A 63-year-old housewife was admitted to hospital on June 21, 1957, for investigation of persistent fever and malaise, which had been present throughout the previous three weeks. She had a history of rheumatic fever when she was 14, 20, and 21 years old, and had since become breathless on exertion. She married at 30 and had since borne three children with normal confinements. At the age of 62 she had a sudden onset of palpitation with dyspnoea, followed one week later by pleuritic pain due to a pulmonary embolus. On examination at that time she was found to have rheumatic heart disease with mitral stenosis and auricular fibrillation, but the liver was impalpable.

Her present illness began on June 1, 1957, with shivering, tiredness, and pyrexia. Prior to admission to hospital she had had persistent fever with an evening temperature of 99–101° F. (37.2–37.8° C.). On admission she looked and felt well, although she had signs of mitral stenosis with auricular fibrillation. The liver was enlarged 8 cm. below the right costal margin, had a smooth surface, and was easily palpable bimanually. The spleen could not be felt. There were no signs of heart failure and there was no anaemia, icterus, palmar erythema, spider naevi, or clubbing.

Investigations.—Liver-function tests: serum albumin, 4.45 g./100 ml.; serum globulin, 4.35 g./100 ml.; electrophoresis indicated an increase in gamma-globulin; serum cholesterol, 184 mg./100 ml.; thymol turbidity, 5 units; thymol flocculation, ++; serum bilirubin, 0.3 mg./100 ml.; alkaline phosphatase, 6.8 units. Her persistent pyrexia was investigated by blood culture, which was negative on five occasions; six catheter specimens of urine were examined with negative results; the Paul-Bunnell test was negative; a cholecystogram and intravenous pyelogram were both normal; her haemoglobin was 13.6 g./100 ml., W.B.C. 6,600 per c.mm., and the erythrocyte sedimentation rate (Wintrobe) 40 mm. in the first hour. Her electrocardiogram confirmed the auricular fibrillation and showed some depression of the ST segment over the left ventricle.

The fever continued in varying degree, once reaching 104° F. (40° C.), and it was occasionally 103° F. (39.4° C.), but usually between 99 and 101° F. (37.2 and 37.8° C.), often reaching normal for some period during the day. It was accompanied by moderate tachycardia. On one occasion (July 16) she developed a transient swelling of the right knee with a small effusion and limitation of movement. Further investigation of the hepatic function during this time showed some deterioration (serum albumin 4 g./100 ml., globulin 3.1 g./100 ml., thymol turbidity 9 units, thymol flocculation +++). She also gradually became anaemic (haemoglobin 8.9 g./100 ml.) without obvious cause, and laparotomy was considered justified in order to determine the exact nature of the hepatic enlargement. Two pints (1,140 ml.) of blood was transfused prior to the laparotomy by Mr. A. J. Heriot on July 26.

At operation the liver was found to be diffusely enlarged, pale in colour, and faintly mottled; the surface was smooth. The spleen was normal on palpation. A wedge of liver was taken for histological examination. Microscopically it showed the normal liver architecture to be maintained, but there was a moderate degree of fatty degeneration. There was no necrosis, fibrosis, or cellular infiltrate (Fig. 1). Following laparotomy the patient was afebrile for three days

but then developed further fever, which persisted for nine days, with a temperature rising to 104° F. (40° C.). One week later, on August 15, there appeared a firm, very tender subcutaneous nodule on the medial side of the right shin, with overlying erythema. The nodule measured 7 by 6 cm., and the overlying skin was lightly attached to it. The following day a similar but smaller nodule appeared on the left buttock, measuring 3 by 3 cm. The erythema gradually faded; there was faint mottling over the nodule on the leg for two days but no residual pigmentation or scarring. Both nodules gradually became less tender. On August 15, 15 days after its appearance, the nodule on the left buttock was excised. Section (Fig. 2) showed the epidermis and dermis to be normal, but the subcutaneous fat included in the section showed changes throughout. These consisted of varying-sized foci of reticulo-endothelial cells lying between the fat cells. These macrophages had a foamy cytoplasm and some were multinucleate. In some areas there were small collections of polymorphonuclear leucocytes and, here and there, considerable numbers of eosinophils. There was no necrosis or fibrosis. The subcutaneous arteries showed a severe degree of obliterative endarteritis.

A second transfusion of 2 pints (1,140 ml.) of blood corrected the hypochromic anaemia. The patient was discharged from hospital on September 17, and has since remained well. There has been neither further panniculitis

FIG. 1.—Liver. (H.E. $\times 125$.) There is moderate to severe fatty degeneration, but no necrosis, fibrosis, or cellular infiltrate.

FIG. 2.—Subcutaneous fat. (H.E. $\times 125$.) Varying sized foci of reticulo-endothelial cells lie between the fat cells. The macrophages have a foamy cytoplasm and some are multinucleate.

nor fever. The liver remained enlarged 6 cm. below the right costal margin, but there has been no worsening of liver function, as indicated by biochemical tests: serum bilirubin 0.3 mg./100 ml.; serum cholesterol, 230 mg./100 ml.; serum alkaline phosphatase, 10.7 units; thymol turbidity, 8.5 units; serum zinc sulphate, 10 units; serum albumin, 3.6 g./100 ml., serum globulin, 4.2 g./100 ml. A needle-biopsy of the liver performed on November 7 showed microscopically no significant change compared with the tissue previously obtained at laparotomy.

Discussion

The common clinical features of the syndrome as it affects the skin have been well recorded, and the title of the disease describes the characteristic triad of pyrexia which varies widely in degree, panniculitis, and the tendency to relapse. The term panniculitis, according to Stockman (1911) and Bain (1912, 1925), was originally introduced by Salin, of Stockholm. By it is meant inflammation of the panniculus adiposus—namely, the superficial fascia of the body covering, which is more or less impregnated with fat. The disease is rare, but widespread throughout the world. Although to date little more than 50 cases have been reported (Shuman, 1951), undoubtedly the disease is much commoner than this would suggest, even allowing for the fact that a number are buried under other names. Obesity is common but not invariable. Most of the reported cases have been in adult women, as in our case, but the disease can also occur in the young, as in the case of a 3-year-old boy described by Sosa Bens *et al.* (1955).

The panniculitis presents as subcutaneous nodules or plaques, adherent to the overlying skin, which appear most commonly on the thigh, although they can involve either extremity and the trunk, particularly over the back and abdomen. They vary in size from a few millimetres to several inches in diameter, characteristically tend to appear in crops, may be painless or tender, and are frequently erythematous, as in our case. There is a tendency for the affected subcutaneous tissue to atrophy, resulting in a depression of varying depth, and often a pigmented scar results. At times these scars may completely disappear spontaneously, as in our case, although this is uncommon. As the title implies, true suppuration does not occur, and the continuity of the skin is almost invariably unbroken, but in a few patients the lesion may become necrotic and break down to discharge a sterile yellow-brown fluid full of fat globules (Beerman, 1953). In some patients the disease is ushered in by an acute attack of nausea, vomiting, and abdominal pain, usually attributed to gall-bladder disease (Koch, 1951), and in many joint pains with swelling and tenderness occur, as in our patient.

The histological changes are non-specific. The process involves the entire subcutaneous fat nodule. DeLor and Martz (1955) recognized three phases histologically. In the first there is an inflammatory reaction in the adipose tissue, with oedema, congestion, and infiltration with polymorphonuclear leucocytes, lymphocytes, and macrophages. The macrophages have been variously called lipophages, histiocytes, polyblasts, granuloma cells, or foam cells. In the second phase there is necrosis of the fat cells and phagocytosis of the fat by macrophages. Sometimes these clump together and their cytoplasm coalesces to form multinucleated giant cells. In the final phase there is atrophy of the fat with connective-tissue replacement, but fibroblastic stimulation is very limited as a rule, although on rare occasions considerable replacement of fat by young connective tissue may occur, as in Christian's original case (his Fig. 8). Vascular changes are uncommon, although both periarteritis and endarteritis may at times be present, and sometimes the latter is considerable, as in our case. Fatty-acid crystals are not seen. Bailey (1937) is of the opinion that a histological feature not previously emphasized is the tendency for the interlobular connective tissue septa to retain the same width throughout.

Involvement of Organs other than Skin

Until recently the disease was thought to be confined to the panniculus adiposus and was therefore mainly of interest to dermatologists. It is true that in most patients the lesion is limited to the skin and is rarely lethal, and, of nine other examples of the disease which we were able to collect, seven of which were confirmed by biopsy by Professor H. A. Magnus, none had evidence of visceral involvement. Even when fatal, death is usually due to intercurrent disease, particularly infection. However, in a few cases not only may various viscera and other organs be involved in the same pathological process, but by being so may result in the patient's death. For cases in which the disease is not limited to the skin Steinberg (1953) has suggested the name "systemic nodular panniculitis," recognizing that it occurs in regions where there is no panniculus but employing the term in default of a better.

We have listed examples where visceral and other involvement has been specifically mentioned, in addition to our own case (see Table). The most extensively involved case which we have been able to find is that of Ungar (1946). It occurred in a woman aged 37 who died of acute suppurative peritonitis for which no local cause could be found, although it was presumed to have come from a

Systemic Weber-Christian Disease

Authors	Organs Involved	Special Symptoms and Signs	Other Remarks
Miller and Kritzer (1943)	Liver, spleen	Died of hepatic insufficiency	First necropsy report: acute focal necrosis of liver and spleen
Baumgartner (1944) Spain and Foley (1944)	" " heart Mesentery, omentum, and peritracheal tissue		Older lesions showed some fibrosis
Friedman (1945) Ungar (1946) Mostofi and Engleman (1947)	Liver, spleen, heart See text Liver, epicardium, peripancreatic, periadrenal, perirenal, and mesentery		
Jones <i>et al.</i> (1950)	Liver		Fatty necrosis and fibrous bands
Hanrahan <i>et al.</i> (1951)	" spleen	Fatal within 3 months of onset	Liver wt. 3,400 g. Severe diffuse fatty metamorphosis
Bjornstad (1951)	" marrow	Macrocytic anaemia	Liver wt. 1,670 g. Numerous rice-sized yellow fatty nodules
Kinmont (1952)	" spleen	Liver-function tests impaired	
Schwartz <i>et al.</i> (1952)	" " heart	Size of liver, spleen, and heart waxed and waned. Systolic murmur, regular rhythm	? Pericardial effusion. No necropsy
Steinberg (1953) Case 1	Peritracheal, pericardial, perihepatic, perirenal, and periadrenal tissue; submucosa of gastro-intestinal tract, bone marrow, mesentery, and omentum		
Case 2	Liver, spleen, periadrenal, perirenal, renal pelvic, myocardial, marrow, and pancreatic adipose tissue		
DeLor and Martz (1955)	Bone	Swollen red painful fingers and toes, with cystic destruction radiologically	Amputation of inflamed right 4th toe
Sattler and Greenberg (1956)	Mainly small-bowel adhesions	Bowel obstruction resulted, tarry stools	Successful resection of 44 cm. of terminal ileum

streptococcal tonsillar infection. In addition to typical skin lesions most of the adipose tissue throughout the whole body was involved, predominantly that of the retroperitoneal space. The pathological process included the true pelvis, mesentery, and omentum, and the lesions were most fully developed in the pararectal, mesosigmoid, mesenteric, and omental adipose tissue and around the kidneys and adrenals. The disease was also found in the anterior inferior mediastinum and in the subepicardial adipose tissue between the root of the aorta and the left auricle. Clinically, she had experienced both precordial and abdominal pain, and per vaginam the pelvic wall was felt to be lined by nodular formations which repeatedly changed in size between attacks of pain.

Hepatic involvement has not been particularly emphasized previously so far as we have been able to ascertain. In any toxic or infective process moderate fatty changes in the liver are to be expected, and, in fact, are commented on by several authors. However, it appears that, quite apart from such relatively slight changes, there is no doubt that occasionally gross fatty metamorphosis can take place in the liver as well as in other organs and give rise to considerable enlargement. Our patient still has enlargement of the liver, but is apparently well and has been afebrile since her discharge from hospital. So far as we have been able to trace, she is the only example where prolonged pyrexia and hepatomegaly preceded the typical skin lesions. Examples of single cases with considerable hepatic enlargement are those of Baumgartner (1944), Friedman (1945), Mostofi and Engleman (1947), Hanrahan *et al.* (1951), and Schwartz *et al.* (1952).

Among causes to which the disease has been attributed are halogens used therapeutically, both bromides and iodides, infections both general and focal, allergy, and trauma, but in most cases there is no obvious cause. Bendel (1949) suggests that the allergy may be bacterial, chemical, or even of virus origin, and that it produces metamorphosis in the fat. This metamorphosed fat then acts as a foreign body in the tissues and calls forth an inflammatory reaction. It does not seem to be a primary disturbance of lipid metabolism, in that almost invariably there are normal values for total blood lipids, cholesterol, and cholesterol ester, and the disease is rarely distributed over most of the body.

Our patient had not received any halogens, we could find no evidence of infection, and trauma could be excluded, for she was under observation in bed at the time of the appearance of the panniculitis. Diabetes mellitus has also been described in association with Weber-Christian syndrome (Machacek, 1948), but her glucose-tolerance test was normal.

The outlook depends chiefly on the causative disease, if such can be ascertained. Remissions can occur. Christian's original patient had a remission of three years' duration, and one patient was free of the disease 20 years after the initial diagnosis—see discussion at the end of the paper by Miller and Kritzler (1943). In the case of Tilden *et al.* (1940), the patient died from miliary tuberculosis. Miller and Kritzler (1943) described the first necropsy to be made in the active stage of panniculitis, and their patient died of general debility with signs of liver insufficiency, and at necropsy acute focal necrosis of the liver and spleen with moderate fatty degeneration of the liver was found. Similarly, Björnstad's (1951) patient died of cirrhosis and fatty degeneration of the liver, accompanied by macrocytic anaemia. In the case of Spain and Foley (1944) death was due to glomerulonephritis. Friedman's (1945) patient died of staphylococcal septicaemia, and Ungar's (1946) patient of streptococcal peritonitis.

From the histological point of view the differential diagnosis is wide, as the microscopical changes are not specific and can result from a variety of conditions causing mechanical or chemical damage to the subcutaneous fat. Many of these can be ruled out clinically from the history alone. Among them may be mentioned subcutaneous fat

necrosis of the newborn, insulin fat atrophy, paraffinoma, ischaemic fat necrosis, and traumatic fat necrosis of the breast. Clinically the syndrome is so characteristic that there are only two other conditions with which it may be reasonably confused, and one of these is probably nothing more than a variant of the disease itself—namely, the Rothmann-Makai syndrome. According to Baumgartner and Riva (1945) this syndrome is more common than Weber-Christian disease, and the patients differ in that they do not have any constitutional upset or pyrexia, and the nodules do not develop in typical attacks or crops and are usually smaller and so deep in the subcutis that they are seldom adherent to the skin and recede without local atrophy. Even so, Beerman (1953) is of the opinion that this distinction is an artificial one. Rare types of thrombophlebitis may also lead to difficulty in diagnosis, as pointed out by Barker (1934), and in such cases it may be necessary to look for histological evidence of thrombosis or inflammatory reaction in the vein wall.

Summary

Attention is drawn to examples of Weber-Christian disease in which, in addition to involvement of the skin, the liver, spleen, heart, bone marrow, and other tissues have been affected.

An example is reported with gross hepatomegaly and anaemia. The visceral involvement appeared eleven weeks before the typical skin lesions, a most unusual feature rendering early clinical diagnosis impossible. During the illness a hypochromic anaemia developed which could not be accounted for other than by the disease itself. At laparotomy severe fatty degeneration of the liver was found. It seems highly probable that the skin and liver were involved in the same pathological process, and possibly the bone marrow also. Her rheumatic heart disease was presumably incidental.

It is suggested that the syndrome may well be a sensitivity response of the reticulo-endothelial system which, although most commonly borne by the skin, can infrequently affect other organs.

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