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WITH DISCUSSION OF SOME OF THE MORE COMMON TYPES

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Xanthoma is defined in Stedman's Medical Dictionary as "A skin disease characterized by the presence of yellow nodules or slightly raised plates in the skin, especially the eyelids." Xanthomatosis is defined as "A generalized eruption of xanthoma, or xanthoma multiplex". The word, however, has come to be used by histopathologists for almost any condition in which foam or xanthoma cells are found. These cells are apparently altered histiocytes or reticulum cells which contain numerous small cholesterol droplets giving the cell a foamy, hazy appearance under the microscope. Under the heading of xanthomatosis, or discussed with them, are several other conditions in which the metabolism of lipids other than cholesterol is primarily involved. The strictest definition of xanthomatosis is a disease, systemic in nature, characterized by the presence of tumor-like masses in the various organs, composed of cholesterol containing xanthoma cells with varying proportions of other connective tissue elements.

PATHOGENESIS OF THE XANTHOMA CELL

Though their origin is still uncertain, they were first observed, and called xanthoma cells, about one hundred years ago. It is possible that a foam cell could result from several possible mechanisms (1):

1. Cholesterol infiltration into the cell is a process which results from an accumulation of cholesterol and cholesterol esters in the serum (hypercholesteremia).

- This hypercholesteremia may be the result of diminished destruction of cholesterol, increased formation of cholesterol, increased formation in the liver and impaired excretion, impaired excretion due to hepatitis, mechanical obstruction of the common bile duct, hyperlipemia or hypothyroidism.

2. Cholesterol accumulation and retention within the cell may originate from an increased synthesis and retention of cholesterol in the cell itself. This process is effected without increased supply of cholesterol and cholesterol esters from the blood stream.

3. Extracellular precipitation or crystallization of cholesterol as it may be observed within the inflamed wall of the gall bladder or the degenerating wallof the arteriosclerotic vessel, and may occur without an increase in cholesterol in the serum. It is due to degenerative changes of the cell.

The first and second mechanism may result in foam cell formation characteristic of the different types of xanthomatoses. As for cholesteroses Thannhauser(1) and Montgomery (2) differ as to the explannation of it; Thannhauser favors the second explanation and Montgomery with some others favor the first.

Another point in the pathogenesis of xanthoma cells is the recognition that certain types of lipidoses may occur with normal cholesterol as well as normal lecithin and neutral fat levels in the serum. This group of xanthomatous disorders, called normo-cholesteremic group, is histologically a granulomatous lesion which in its later stages shows accumulation of foam cells in the lesion.

As Beerman(3) states, the basic mechanism under-

lying the development of the xanthomatoses is complex and little understood. It is obvious that there is no singel etiologic concept for all types. Various explanations include the role of the liver in the synthesis, a pituitary factor, hormones from various organs, such as the pancreas and thyroid gland, vitamin deficiencies, involvement of cutaneous nerve sheaths, improper elimination of lipids, and imbalance between the ratio of various lipids. Irritation undoubtedly plays some role in certain of the locallipidoses.

The relationship of Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granulomas of bone has been considered by many to be not three different diseases but rather one disease with three different phases, constituting a disturbance of the reticulo-endothelial system(4-17). Four phases as these diseases characterize are given by Engelbreth-Holm, Teilum and Christiansen(18):

1. A proliferative phase in which histiocytic proliferation with accumulation of eosinophilic histiocytes is observed. There is no evidence of foam cells in this phase.
2. A granulomatous phase with increase in blood vessels and fibrils, reticular cells and histiocytes, eosinophils and giant cells (Touton Cells) and incipient accumulation of lipids in macrophages.
3. A xanthomatous phase with nests and isolated cells.
4. A fibrous stage considered as a healing phase.

Most of these phases overlap with no strict separation of histologic features. It is also suggested by Thannhauser that there may be a close relationship of juvenile xanthoma (Nevoxanthoendothelioma) to the system-

ic lesions of Hand-Schüller-Christian syndrome (involvement of internal organs) and that nevoxanthoendothelioma seems to be the monosymptomatic variety of this disease in infants, involving only the skin, and with good prognosis.

CLASSIFICATION OF XANTHOMATOUS DISEASES AND ALLIED CONDITION

I Hypercholesteremic xanthomatosis

- A. Essential xanthomatosis of the Hypercholesteremic type.
  1. Xanthelasma of the eyelids and xanthoma et planum.
  2. Tendon xanthoma
  3. Xanthoma tuberosum et planum and tendon xanthoma.
  4. Xanthoma of the blood vessels and endocardia.
  5. Familial hypercholesteremic. "Forme fruste" of essential xanthomatosis of the hypercholesteremic type.
- B. Hypercholesteremic Xanthomatosis secondary to Liver Disease.
  1. Xanthomatous biliary cirrhosis. Pericholangiolitic biliary cirrhosis with tuberous and plain skin xanthoma.
  2. Rare cases of chronic liver disease with secondary xanthomatosis.
     a. Hemochromatosis, hypercholesteremic and skin xanthoma.
     b. Post-operative obstruction of the common bile duct, hypercholesteremic and skin xanthoma.

C. Hypercholesteremia in Hypothyroidism

II Hyperlipemia with secondary Eruptive Xanthoma

A. Idiopathic hyperlipemia with secondary eruptive xanthoma.

1. Idiopathic (familial) hyperlipemia in children with hepatosplenomegaly and secondary xanthoma.
2. Idiopathic hyperlipemia in adults with secondary eruptive xanthoma occasionally accompanied by glycosuria and hepatosplenomegaly.

B. Symptomatic Hyperlipemia with Secondary Eruptive Xanthoma

1. Hyperlipemia in severe untreated diabetes with secondary eruptive xanthoma.
2. Hyperlipemia in chronic pancreatitis and eruptive xanthoma.
3. Hyperlipemia in glycogens storage disease (Von Gierke's disease) and eruptive xanthoma.
4. Hyperlipemia in lipid nephrosis.

III Normocholesteremic Xanthomatoses

A. Eosinophilia Xanthomatous Granuloma Synonymous with Hand-Schüller-Christian syndrome. Essential xanthomatosis of the normocholesteremic type, Lipid Granulom, Eosinophilic granuloma.

1. Skin manifestations of eosinphilic xanthomatous granuloma (Hand-Schüller-Christian syndrome).
   a. Xanthoma disseminatum of the skin.
   b. Petechiae-like lesions of the skin in eosinophilic xanthomatous granuloma Hand-Schüller-Christian syndrome).

2. Diabetes insipidus and xanthoma disseminatum of the skin.
3. Eosinophilic xanthomatous granuloma of the bone (eosinophilic granuloma of bone, osseous xanthoma).
4. Hand-Schüller-Christian syndrome; osseous lesions of eosinophilic xanthomatous granuloma (defects in the membranous bones of the skull, exophthalmos and diabetes insipidus).
5. Generalized form of eosinophilic xanthomatous granuloma (generalized lipid granulomatosis, generalized xanthomatosis of the normocholesteremic type, generalized form of Hand-Schüller-Christian syndrome, acute reticuloendotheliosis).

B. Xanthoma Cells in Inflammatory tissue and in True Tumors.
   1. Xanthoma cells in inflammatory tissue.
      a. Inflamed tissue showing xanthoma cells.
      b. Inflammatory xanthoma of the breast.
      c. Xanthoma cells in osteitis fibrosa cystica disseminati (fibrous dysplasia).
      d. Xanthomatous transformation of the mesentery and intestinal lipodystrophy of Whipple.
      e. Xantholipomas
   2. Xanthoma cells in tumors
      a. Nevoxanthoendothelioma
      b. Xanthomatous polycystic lymphangiomas
      c. Single xanthomatous giant cell tumor
      d. Epithelial tumors with xanthoma cells

C. Supplement

1. Lipoid proteinosis
2. Necrobiosis lipoidica diabeticorum.

SOME OF THE MORE COMMON XANTHOMATOUS CONDITIONS

I Hypercholesteremic Xanthomatosis

A. Primary Essential Xanthomatosis(19-22)

Thannhauser(23) states that essential xanthomatosis is a heredo-familial constitutional disorder of intracellular metabolism of reticuloendothelial cells and histiocytes, characterized by an increase in cholesterol and cholesterol esters within the cells. He divides essential xanthomatosis into two types: the hypercholesteremic type, characterized by high serum cholesterol and involvement of the skin, tendons and tendon sheaths, liver, bile ducts, gall bladder, endocardium, and blood vessels, and the normocholesteremic type characterized by normal serum cholesterol and involvement of the skin, bones, brain, dura, pleura, lung, lymph nodes, and spleen. It is now thought by many that the normocholesteremic type cannot be classified with essential xanthomatoses. Histologically the lesions of the two types are similar, that is, foam cells filled with cholesterol, inflammatory cells, fibroblasts, and giant cells. There is no extracellular deposit of lipid.

The hypercholesteremic type of xanthomatosis has been described all over the world and in all races. It is found predominantly in white people, and the incidence in Jews seems to be higher. It is equally distributed between the sexes and occurs in all ages. The onset is usually insidious and the disease is often brought to light by the dysfunction of some internal

organ. The progress of the disease depends on the organs involved. Small xanthelasma may me present for a lifetime without change. The xanthomata of essential xanthomatosis rarely change, but may eventually disappear and be replaced by scar tissue. Xanthelasma of the eyelids usually develop in the fourth decade and grow slowly. They do not signify involvement of other organs. Particularly if the serum cholesterol is normal, it may be assumed no other organs are involved. The typical skin manifestation in this condition is xanthoma tuberosum et planum. These are xanthomatous tumors and plaques located on the extensor surfaces of the extremities, especially the elbows, knees, and buttocks. They do not usually occur in the flexor folds. There is usually high serum cholesterol and occasionally slight elevation in the neutral fat, but not enough to make the serum milky. Once these tumors have formed they are usually static and do not disappear. Tendon xanthomata occur usually on the Achilles tendon, on the finger tendons, and around the knee joint. If the blood cholesterol is normal there is usually no other organ involvement. In adults solitary tendon xanthomata may occur. In children they are frequently associated with xanthoma tuberosum et planum. Xanthomatous changes may occur in the walls of the bile ducts which cause thickening, obstruction, and dilatation, due to xanthomata themselves and to xanthomatous scarring. The gall bladder may be involved. This leads to xanthomatous biliary cirrhosis which is usually associated with xanthoma tuberosum et planum on the elbows, knees, and buttocks, and also xanthomatous changes in the creases of the palms of the hands. Due to the biliary cirrhosis in this condition there may be hyperlipemia in addition

to the primary xanthomatosis, secondary xanthomatosis may develop which lesions occur in crops, are transient, and fluctuate according to the level of the serum neutral fat. A constant symptom in xanthomatous biliary cirrhosis is jaundice which lasts for many years. This subject is taken up more fully later in this paper.

The association of xanthoma tuberosum et planum with hypercholesteremia, cardiovascular disease especially coronary artery disease, and sudden death has long been recognized. There may be xanthomatous involvement of the endocardium, heart valves, coronary arteries, great vessels, and peripheral vessels. The histologic picture is hyperplasia of the intima with groups of typical foam cells under the endothelium. This may cause bizarre murmurs, congestive failure, angina, coronary occlusion with myocardial infarction in children as well as in adults. It has been suggested that hypercholesteremia may be the common denominator of all coronary arter disease. It is thought by some that the primary disorder in this disease is not in the reticuloendothelial cells themselves, but in cholesterol metabolism, and that these cells simply phagocytose cholesterol because of the high serum level which is due to some defect in cholesterol metabolism. They feel that there may be increased formation of cholesterol by the liver and that the body is not able to excrete it. Whatever thecause, there are many who believe that the chief characteristic of the disease is hypercholesteremia which is found in many people who are symptom free. The next most frequent manifestation is coronary artery disease, then xanthelasma and arcus senilis. The most infrequent manifestations are xanthoma tuberosum et planum, xanthoma tendonosum, and xanthomatous

biliary cirrhosis. Families of people who have xanthomatosis have been studied and a great number of symptom free relatives have been found to have hypercholesteremia as well as relatives who have stigmata of xanthomatosis. It is definitely established that the disorder is hereditary, but the mode of transmission is in dispute. There are those who feel that it is a recessive trait and those who feel that it is a dominant trait, the chief characteristic being hypercholesteremia, the full syndrome being much rarer. There is good evidence to the effect that it is an "incomplete" dominant trait. That is to say that hypercholesteremia represents the heterozygous abnormal condition, that is the person who carries two tainted genes. The frequency and linkage relations are not understood. Hypercholesteremic people seem to have much greater fluctuations of the cholesterol level than normal people. Normal people will consistently have the same level, while hypercholesteremic people will have levels that vary greatly depending on diet and other unknown factors. In hypercholesteremics the amount of cholesterol above the normal level seems to have little influence on whether manifestations of xanthomatosis develop or not. The manifestations may develop at low hypercholesteremic levels or be absent at extremely high hypercholesteremic levels. Treatment is directed at dietary abstinence from cholesterol.

B. Hypercholesteremic Xanthomatosis Secondary to Liver Disease

The term "xanthomatous biliary cirrhosis" was used originally(24) to designate a clinical syndrome in which xanthomatous change in the liver was but one of its most conspicuous features. The characteristics of

this syndrome(25) were:

1. Skin xanthoma of the "plain and Tuberous" variety.
2. Enlarged liver and spleen.
3. Obstructive type of jaundice of years' duration.
4. Extremely high values for total cholesterol as well as for lecithin.
5. The serum is transparent and not creamy despite the outstanding increase of cholesterol and lecithin. Low values for neutral fat in the serum are found also.

It is to be understood that the changes throughout the liver were considered to be but one component of a systemic disease and not the cause of the syndrome.

The histological picture is interesting in that no foam cells were observed in the liver of patients, but, instead, there was cirrhosis of the liver caused either by cholangiolitis or by extrahepatic obstruction. The one fundamental histologic finding common in these cases was a chronic inflammatory(26) reaction in the interstitial portal area. It has been found by MacMahon and Thannhauser(27) that the marked accumulation of cholesterol and lecithin at the beginning of xanthomatous biliary cirrhosis is probably not only the result of a retention of bile but also the consequence of an imbalance of increased cholesterol and lecithin production and an inadequate excretion of these substances.

The onset of this disease is insidious and there is no evidence that heredity(28) plays any role. The patients complain of itching of the skin, which is speedily followed by jaundice of the obstructive type, i.e, bilirubin giving the direct and indirect van den Bergh reaction is found in the serum. The jaundice remains till the fatal end of the disease. The grade of the jaundice does not vary much during the course of

the disease and seems rather independent of the development of the skin xanthomas(29) and of the fluctuation of the cholesterol and lecithin values in the serum. Fever or chills are not a feature of this disease. The skin xanthoma may appear simultaneously with the jaundice or in most cases develop many months later. The tuberous deep yellow xanthomas are observed on the face, on the elbows, arms, fingers, buttocks, and distal parts of the lower extremities. Plain xanthomas appear on the eyelids and the creases of the hands. The location of the skin xanthoma is different from that in the so-called "disseminata" type of xanthoma characteristic of "normocholesteremic xanthomatosis", as seen in Hand-Schüller-Christian disease. In this latter entirely different type of disease the xanthoma are light yellow or deep sepia brown, disseminated around the neck and the trunk and arranged in linear clusters in the axilla. The skin xanthomas in xanthomatous biliary cirrhosis persist during the entire course of the disease. The liver and spleen also remain large. The surface of the liver is very firm but not nodular. Ascites is not a feature of this disease. Sometimes a peculiar maculo-pustular eruption, which appears and disappears intermittently, is seen all over the body, and especially the trunk and legs. The eruption is inflammatory in nature and does not contain foam cells.

Analysis of the serum lipids provides the most decisive finding for diagnosis. The serum is transparent and not creamy throughout the disease. The typical cholesterol and lecithin syndrome findings are always seen. Prothrombin time in the first years is normal. Later hemorrhages in the gums and vomiting of blood from ruptured varicies occur. Profuse hemorrhage from

esophogeal varicies is the most common terminal event. Liver function tests are not of great value for the diagnosis of xanthomatous biliary cirrhosis since the clinical syndrome is typical in all cases, namely: 1. Skin xanthoma of the "plain and tuberous" variety, 2. Enlarged liver and spleen, 3. Obstructive type of jaundice of years' duration, 4. Extremely high values for total cholesterol as well as for lecithin, 5. The serum is transparent and not creamy despite the outstanding increase of cholesterol and lecithin. Low values for neutral fat in the serum are also found.

II Secondary Xanthomatosis Due to Hyperlipemia(30-31)

Secondary xanthomatosis or the eruptive form of xanthoma is not a disease entity, but is a symptom of hyperlipemia, which itself may be due to many different causes. In secondary xanthomatosis the lesions are not constant as in primary xanthomatosis, but appear and disappear depending on the level of the hyperlipemia. They may appear anywhere on the body. The serum is milky due to the great increase in neutral fat. Cholesterol and lecithin are not increased in the same proportion as the neutral fat. In primary xanthomatosis the serum is clear and the only lipids in abundance are cholesterol and sometimes lecithin. Histoligically the lesions of secondary xanthomatosis show extracellular fat deposits, occasional foam cells, and do not show granulomatous formation with giant cells. The inflammatory reaction is prominent. Secondary xanthomatosis may develop during the course of primary xanthomatosis.

Idiopathic familial hyperlipemia with hepatosplenomegaly and secondary xanthomatosis has been described by a number of authors and it has become apparent that

the eruptive xanthomata may be present or absent, fluctuating in the same individual depending on the level of the hyperlipemia. Typical of secondary xanthomatosis the lesions show inflammatory tissue and extracellular fat deposits, few if any foam cells and no granulomatous tissue. The liver and spleen are greatly enlarged due to fat deposition. A few foam cells are found in the liver, spleen, and bone marrow. These are thought to be due to phagocytosis of lipids as a result of hyperlipemia, not to a disorder in the cells themselves. The cause of this condition is not known, but the hyperlipemia can be lowered somewhat by a diet free of fat and cholesterol. Since the extrinsic fat supply is not greater than normal, it is believed that the hyperlipemia may be due to a defect in the mechanism of fat deposition. The giving of choline or lipocaic has no beneficial effects. The skin lesions may be nodular or vesicular and may occur anywhere on the body and in the mouth. The disease is characterized by the appearance and disappearance of skin xanthomata and by episodes of colicky or dull steady abdominal pain with fever and leucocytosis. Initially in these attacks the fat level of the blood is high, the retinal vessels appearing to contain milk, and as the fat level drops the attack subsides. Following each attack the liver and spleen become large and remain so for several weeks and then may become reduced in size if the blood fat level is kept low. Abnormalities have not been noted in the urine and stool. It is presumed that the high level of blood fat during an attack is lowered by deposition of fat in the liver and spleen, not by excretion. No jaundice has been noted. Blood sugar and NPN are normal. The disease is very slowly progressive and

usually death results from some other cause. The scarcity of autopsy material makes it difficult to state the amount of permanent damage done to the liver.

Secondary xanthomatosis occurs in diabetes mellitus when there is hypercholesteremia, and hyperlipemia. It occurs in poorly controlled diabetics with fatty livers. The skin manifestations and hyperlipemia are usually cleared by the proper use of insulin. Histologically the lesions are typical of secondary xanthomatosis. They may appear anywhere on the body, but are usually over pressure points and on extensor surfaces. Diabetics with hypercholesteremia and hyperlipemia show a marked degree of atherosclerosis. Treatment consists of controlling the diabetes. Diabetes may be associated with hypercholesteremic xanthomatosis when there is xanthomatous invasion of the pancreas. In chronic pancreatitis there may be hyperlipemia with secondary xanthomatosis. The resulting xanthomata are typical of secondary xanthomatosis. In acute pancreatitis there may be marked hyperlipemia, but eruptive xanthomata have not been reported in cases which have not had a prolonged hyperlipemia.

In Von Gierke's disease (glycogen storage disease) there is often hyperlipemia with secondary xanthomata. There is enormous enlargement of the liver without enlargement of the spleen. The liver cells are filled with glycogen and also contain a large amount of neutral fat. All organs of the body show increased glycogen and fat, especially the liver and kidneys. It is thought to be due to an intracellular metabolic disturbance in the phosphorylase-phosphatase system which upsets the balance of the synthesis and degeneration of glycogen. Consequently utilizable sugar is available

only in small amounts. Attacks of hypoglycemia are frequent. Probably due to this upset in carbohydrate metabolism there is increased fat storage in the liver, hyperlipemia, and ketosis. The greater the glycogen storage the worse becomes the hyperlipemia. The serum is milky and the blood sugar is low. There is acetonemia and acetonuria. These children have fat cherubic faces, large abdomens and thick extremities. The resulting xanthomata are typical of secondary xanthomatosis. Most cases are fatal although recoveries have been reported. There is no therapy, but because of the hyperlipemia a diet low in fat is recommended.

III The Normocholesteremic Type(4-17)

About the group of diseases classified by Thannhauser as the normocholesteremic type of primary essential xanthomatosis there is a gread deal of disagreement. It is thought by many that these diseases are not essential xanthomatoses at all. Clinically there is no resemblance to the hypercholesteremic type. In this group of diseases there is no hereditary or familial factor. The serum cholesterol is normal or high normal with normal ratio of free cholesterol to cholesterol esters. The skin may show xanthoma disseminatum. The organs involved are the skin, bones, chiefly long bones, and skull, bone marrow, dura, brain, liver, lymph nodes, and spleen. The only resemblance to the hypercholesteremic type is the finding of typical foam cells filled with cholesterol in the lesions. The diseases or syndromes to be discussed in this group are Hand-Schüller-Christian disease, Letterer-Siwe disease, and eosinophilic granuloma of the bone. They are diseases of the reticuloendothelial system of unknown cause. Whether they are different manifestations of

the same disease, related diseases, or entirely separate diseases remains to be seen. Clinically the three diseases have many things in common as well as many dissimilar features. Histologically the lesions show great similarity, which may be due to the fact that it is the reticuloendothelial cells which are involved in each.

A. Eosinophilia Xanthomatous Granuloma Synonymous with Hand-Schüller-Christian syndrome. Essential xanthomatosis of the normocholesteremic type, Lipid Granuloma, Eosinophilic granuloma.

Hand-Schüller-Christian disease was first known by the triad of Christian which is exophthalmos, diabetes insipidus, and defects in the skull. It is now agreed that the diagnosis does not rest on this triad. The lesions are granulomatous with typical foam cells containing cholesterol, histiocytes, and fibrous tissue. Skin lesions occur in about one half of the cases. They may be of different types. There may be bronzing of the skin andblotchy pigmentation, xanthelasma, xanthoma disseminatum, granulomatous ulcers, seborrheic dermatitis, and scattered small yellow macules which are minute xanthomata. Xanthoma disseminatum may occur without evidence of systemic disease. Xanthomatous nodules appear in the axilla, sides of the neck, anticubital fossa, groin, and behind the knees. They may extend down the chest and down the arms, but are on the flexor surfaces. There may also be lesions in the mouth, pharynx, larynx, trachea, and on the conjunctiva and cornea. The bones may be involved with typical granulomatous lesions, especially the long bones, skull, ribs, scapulae, and pelvis. By x-ray these appear to be round, ovalor irregular punched out areas. In the skull the lesions may erode through the outer table causing bumps on the

head, and even erode through the skin causing draining granulomatous ulcers. It is not uncommon to have the mastoids involved causing mastoiditis, otitis media, and draining ears, and the sinuses causing sinusitis. The orbits are often invaded by xanthomatous tumors causing mechanical exophthalmos. The base of the skull may be involved disturbing the posterior pituitary causing diabetes insipidus. Also the dura may be involved damaging the subthalamic region and the pituitary stalk. The pituitary and the tuber cinereum may be directly involved. These patients can produce urine which concentrates to specific gravity 1.010 which is not typical of diabetes insipidus, but there is marked polyuria and they are benefitted by posterior pituitary extract. The jaw bone may be involved causing loosening and falling of the teeth. The liver and spleen are enlarged by nests of xanthoma cells scattered through them, but there is usually no biliary obstruction or jaundice. The lymph nodes may become enlarged due to nests of xanthoma cells. The lungs may become involved and show xanthomatous changes in the septal cells of the alveoli. The x-ray appearance may resemble miliary tuberculosis. Pulmonary fibrosis and cor pulmonale may develop. There may be xanthomatous tumors on the pleura and pertoneum. There may be bizarre endocrine symptoms because of mechanical disturbance of the endocrine glands. The serum cholesterol is normal and there is no elevation of neutral fat so the serum is not milky. The disease has been reported in all races. It may occur from infancy to middle age although it is most common in children. It may run a chronic course or a rapidly fatal course. Reportedly thirty percent recover and the granulomas disappear and are replaced by fibrous

scar tissue.

The disease cannot be definitely diagnosed clinically because it may be indistinguishable from Letterer-Siwe disease, but must be diagnosed histologically by the presence of granulomas with an abundance of foam cells filled with cholesterol. There is no treatment for Hand-Schüller-Christian disease.

Letterer-Siwe disease is a disease of the reticuloendothelial cells and histiocytes which is manifested by enlargement of the spleen and liver, a hemorrhagic diathesis, petechial rash, progressive anemia, and enlargement of lymph nodes. It is not familial or hereditary. It occurs usually in infants but may occur in children. It runs a rapid course usually a few weeks but may last as long as two years, and it is fatal. The onset may be with some infection such as otitis media, and because of this it has been called infectious reticuloendotheliosis. However, the initial infection is probably secondary and simply brings to light the already existing disease.

The histological lesions consist of granulomas with an abundance of histiocytes and non-lipid starting macrophages. There may be occasional eosinophiles. They resemble the lesions of Hand-Schüller-Christian disease, but there are not foam cells present usually, and if they are present they are scarce, not abundant. Letterer-Siwe disease has been called non-lipid reticuloendotheliosis, and Hand-Schüller-Christian disease has been called lipid reticuloendotheliosis.

Almost all cases show skin lesions which may be purpuric spots or may look like seborrheic lycema. Usually the child runs a febrile course and often there is associated leucocytosis. There may be marked enlarge-

ment of the spleen and liver. The spleen is almost entirely replaced by proliferating histiocytes. There is replacement of the bone marrow and anemia and thrombocytopenia. The lymph nodes are generally enlarged by the invasion of histiocytes. The bones, especially the long bones and the skull, may show round, oval or irregular punched out areas similar to Hand-Schüller-Christian disease. The nodules of histiocytes may and do occur anywhere in the body. The thymus, endocrine glands, pancreas, gastrointestinal tract, lungs, dura and kidneys, particularly are involved. The base of the skull may be involved and give the typical triad of Christian. There is a generalized hyperplasia of the reticuloendothelial cells all over the body. The serum cholesterol and neutral fat are normal and the serum is not milky. There is no treatment. The diagnosis must be made histologically because clinically it may resemble Hand-Schüller-Christian disease.

Eosinophilic granuloma of bone is a disease of children, adolescents, and occasionally young adults. It may occur singly in one bone or in many bones at the same time. The serum cholesterol is normal. It may be an asymptomatic disease diagnosed accidentally by x-ray, or there may be pain and swelling over the affected part with fever and leucocytosis. Occasionally there is a two to four per cent eosinophilia in the periferal blood. Cases have been reported with skin manifestations similar to Letterer-Siwe disease.

The onset may be abrupt or insidious. Any bones but those of the hands and feet may be involved, but the commonest sites are the skull, ribs, pelvis, and long bones. By x-ray the lesions are round, oval, or irregular cystlike areas. The cortex of the bone may

become eroded. In cases of multiple lesions some may be healing while new ones are developing.

Histologically it is a granuloma with a heavy infiltration of eosinophiles, with numerous histiocytes and non-lipid containing macrophages, and a rather marked inflammatory reaction. There are no foam cells except an occasional few which are thought to be due to secondary deposition of cholesterol.

Eosinophilic granuloma is not a systemic disease, but limited to the skeleton. The lesions often heal spontaneously, and also respond well to curettage or x-ray treatment. It may heal completely leaving fibrous scar tissue. By x-ray there may be no evidence of there having been disease of the bone. Eosinophilic granuloma of the skin is histologically similar to eosinophilic granuloma of the bone, but is thought to be a totally unrelated disorder, however, in the skin lesions there may be occasional foam cells. These are thought to be local cholesterol deposits.

No virus or bacterium has been cultured from the lesions of these three diseases. The cause is not known. They are all manifested by a hyperplasia of reticuloendothelial cells and histiocytes. Some observers believe that they are all different manifestations of the same disease. Thannhauser says that the natural history of eosinophilic granuloma has four stages: 1. proliferative stage, in which there is histiocyte proliferation, and an accumulation of eosinophiles, and there is no evidence of foam cells; 2. granulomatous stage, in which there is an increase in blood vessels, reticular cells and histocytes, eosinophiles and giant cells, and insipient lipid phagocytosis; 3. xanthomatous stage,

in which there are isolated foam cells as well as nests; 4. fibrous stage, which is the healing stage with replacement of the granuloma by fibrous scar tissue. There is often no strict demarkation and the histologic features of the stages may overlap during the course of the disease. He feels that eosinophilic granuloma is the monosymptomatic early stage of Hand-Schüller-Christian disease which may heal or go on to the classical picture. Many observers feel that the cholesterol in the foam cells of Hand-Schüller-Christian disease is secondary to the disturbance in the reticuloendothelial cells. There have been cases of Hand-Schüller-Christian disease in which most of the lesions have contained typical foam cells, but a few have been non-lipid reticular granulomas as seen in Letterer-Siwe disease. There are cases in which a biopsy taken early in the disease showed non-lipid reticular granuloma, and later autopsy of the lesions showed the typical foam cells of Hand-Schüller-Christian disease. Also there are cases from which a biopsy showed typical foam cells, which have healed, the xanthomatous lesions being replaced by fibrous scar tissue.

Histologically the lesions in Letterer-Siwe disease and Hand-Schüller-Christian disease are much alike except for the cholesterol filled foam cells. In lesions where cholesterol is absent they may be indistinguishable. Wallgren(32) feels that they are the same disease. He feels that the cholesterol in the foam cells is secondary to the formation of reticuloendothelial granulomata and is probably deposited sometime after the granulomata are formed. When the disease runs a rapid course as in Letterer-Siwe, cholesterol has not yet accumulated, and when there is a more chronic

course as in Hand-Schüller-Christian disease Cholesterol is accumulated. Foam cells are rearely found when the disease lasts less than three months and are always found when the duration is more than twelve months.

Letterer-Siwe disease tends to involve infants and young children, while Hand-Schüller-Christian disease involves slightly older children and may be found in adults. The cases of Hand-Schüller-Christian disease which most resemble Letterer-Siwe disease occur in infants. Neither disease has any characteristic feature which cannot occur in the other. Wallgren explains the apparent differences on the age of the patients affected and the rapidity of the course. He believes that they are the same disease and that the fundamental pathology is a granulomatous proliferation of the cells of the reticuloendothelial system which occurs for an unknown reason.

Farber(33) believes that eosinophilic granuloma of bone is a monosymptomatic stage of Hand-Schüller-Christian disease which heals without ever becoming systematized.

Lichtenstein and Jaffe point out the marked dissimilarity between eosinophilic granuloma and Letterer-Siwe disease, the first being a benign usually self limited disease limited to the skeleton, and the second a rapidly fatal disease involving all organs of the body. However, they also point out that histologically, early Letterer-Siwe disease may resemble eosinophilic granuloma and late it may resemble Hand-Schüller-Christian disease. Eosinophilic granuloma in healing may pass through a stage resembling the lipogranuloma of Hand-Schüller-Christian disease.

The four stages in the development of eosinophilic

granuloma suggested by Thannhauser are thought by some to apply to all three diseases. Eosinophilic granuloma may heal without passing through the granulomatous stage. Letterer-Siwe disease often does not last long enough to develop the xanthomatous stage and the fibrous stage. Hand-Schüller-Christian disease is usually seen in the xanthomatous stage, but occasionally in the late granulomatous tage, and may pass into the fibrous stage. In spite of these apparent similarities in the three diseases the underlying cause is not known and they still may be three entirely separate diseases with some manifestations in common. All that can be said at present is that they are diseases manifested by proliferation of reticuloendothelial cells due to an unknown cause and that probably the accumulation of cholesterol is secondary, which removes them from the classification of primary essential xanthomatosis.

B. Xanthoma Cells in Inflammatory Tissue and in True Tumors

Xanthomatous tumors and xanthoma cells in inflammatory tissue(35) have been noted. There is no hyperlipemia. Thannhauser believes that these are not evidence of systemic primary essential xanthomatosis, nor of xanthomatosis secondary to hyperlipemia. He believes that there is a local disturbance in lipid metabolism limited to the tumor or inflammatory area. Typical foam cells are present, but not in great numbers. It may occur in any chronically inflamed area such as chronic salpingitis, old absecesses, and chronic osteomyolitis.

Xanthomatous tumors may occur in the breast. Xanthomatous changes in the mesentary have been described in the areolar tissue and lymph nodes. Xantholeomata

have been reported intra-abdominally and around joints which have occasionally become liposarcomas. Various types of tumors have been reported which contain foam cells including carcinoma of the uterus, carcinoma of the prostate, and hypernephroma.

IV Allied Conditions

A. Gaucher's Disease(36-38)

Gaucher's disease and Niemann-Pick's disease are not xanthomatoses, but are among the essential lipidoses. Gaucher's disease is rare familial systemic disorder of intracellular metabolism of reticuloendothelium and histiocytes. The cerebroside, kerasin, is accumulated in the cells. Thecause is not known. The values of kerasin in the serum are normal. All races are affected and the occurance is questionably higher in Jews. There is tremendous enlargement of the spleen, infiltration of the bone marrow, anemia, thrombocytopenia, skeletal defects, moderate enlargement of the liver and lymph nodes, thickening and brownish discoloration of the conjunctivae, and blotchy pigmentation of the skin.

The chief pathology is caused by cells of the reticuloendothelial system which are greatly swollen with kerasin, called Gaucher foam cells. The splenic pulp is almost entirely replaced by alveolar spaces containing nests of Gaucher cells. The bone marrow is largely replaced by Gaucher cells, and there may be erosion and thinning of the cortex, especially of the long bones. The lymph nodes are also involved, but usually only the internal ones, not the superficial. Gaucher cells are found in the liver, but not in as great numbers as in the spleen. There are two types of Gaucher's disease, the adult form which is an insidious and chronic dis-

ease, and the infantile form which is an acute fulminating disease.

The adult form may begin at any age from childhood to as late as the age of fifty, but due to the vague onset it is difficult to state exactly when it begins. In this form the disease is limited to the reticuloendothelial cells of the lymphatic and hematopoietic systems.

Bone pain and fever are often the first symptoms. Usually by the time there are symptoms the spleen has enlarged. Patchy pigmentation on the face or a bleeding tendency may be the first thing noted. The disease usually has remissions and exacerbations and often the patients live many years and die of some unrelated disorder. The spleen may become so large that it causes protrusions of the abdomen and displacement of other organs. For purely mechanical reasons the spleen is sometimes removed. The liver is usually enlarged but function is not impaired. There is no jaundice. The intermittent attacks of severe prostrating bone pain are the most outstanding clinical feature of the disease. There is decalcification and thinning of the cortex so that the long bones have a moth eaten appearance, but spontaneous fractures are rare. There may be, however, destruction of vertebral bodies with collapse. Due to the replacement of the bone marrow by Gaucher cells and probably also to the replacement of the spleen, there is progressive anemia and leucopenia.

As the disease progresses there may develop a serious thrombocytopenia with hemorrhagic tendency. Splenectomy sometime improves the blood picture. Small wedge shaped areas of brownish discoloration may develop in the exposed part of the conjunctiva from the canthus to the limbus. Also exposed skin areas frequently become darkly pigmented with melanin. There is no lipemia or hypercholesteremia. Bone marrow biopsy and

demonstration of Gaucher cells with establishe the diagnosis.

Prognosis depends on the course and the age of onset. It is poor when the onset is in the first decade and improves to the point of being good when the onset is in the third decade. There is no cure. Treatment is only symptomatic such as blood transfusions, splenectomy, and irradiation of bones during episodes of pain.

The acute infantile fomr of Gaucher disease is very rare. It usually has its onset in the first year of life, occasionally in the second. It is fatal, however, the patient last from two to six months. The Gaucher cells are not limited to the reticuloendothelial cells of the lymphatic and hematopoietic systems, but are found in many organs of the body. These children show all the abnormalities of the adult form except the pigmentation. In addition there are neurological signs with spasticity, opisthotonus, and mental deterioration. There is progressive cachexia and there are episodes of laryngospasm with cyanosis. This latter is the usual immediate cause of death.

Nests of Gaucher cells are found in the spleen, bone marrow, liver, and lymph nodes, and as well in the lungs, intestines, adrenals, and thymus. Typical Gaucher cells are not found in the brain. The pyramidal cells of the cerebral cortex show degeneration. There are vacuoles in the cytoplasm and the projections are retracted. The ganglion cells are necrotic and persist in a mummified state. Around these areas there is proliferation of glial cells. There is no treatment.

B. Niemann-Pick Disease(39-41)

Niemann-Pick disease is a rare congenital familial

systemic disorder of intracellular metabolism of reticuloendothelial cells and histiocytes in any and all organs in which there is an accumulation of the diamino phosphatide, sphingomyelin.

The cause is not known. The disease occurs primarily in females (five to one) and primarily in Jews (three to one). It is often associated with other manifestations of congenital degenerative disease. It occurs in all parts of the world and starts in infancy. No cases have lived beyond the second year.

The disease causes enlargement of the liver, spleen, and lymph nodes, diffuse pigmentation of the skin, bluish-black pigmentation of the mucous membranes of the mouth, gastrointestinal symptoms, mental and physical deterioration, amaurosis, hypertonicity, emaciation, cachexia, and death.

The Niemann-Pick cells are foam cells containing sphingomyelin but are not surrounded by granulomatous or inflammatory tissue. The cells may be found anywhere in the body where there are reticuloendothelial cells and histiocytes. The phosphatide and cholesterol content of the serum in not elevated. Neutral fat is increased especially as the disease progresses and the serum may be milky.

Microscopically every organ in the body is involved especially the gastrointestinal tract, endocrine glands, and lungs. The changes in the brain are comparable to those in Tay-Sch disease. The ganglion cells are greatly enlarged and there is marked gliosis of the cerebellum. A cherry red spot may be seen in the macula.

The onset is usually in the first few months of life. It is insidious and the first symptoms are gastrointestinal such as anorexia and vomiting. The ab-

domen enlarges and the extremities become thin with complete loss of subcutaneous fat. There is increased melanin in the skin and mongoloid spots and facies. The bones show patchy areas of reabsorption. There is generalized lymphadenopathy. X-ray of the lungs shows a picture resembling miliary tuberculosis. Breathing is difficult because of pulmonary infiltration. There may be high fever during the course of the disease. Due to involvement of the central nervous system, there is a slight increase in the reflexes, weakness, deafness, and blindness. The infant soon becomes an idiot and has a progressive downhill course to death. There is no treatment.

SUMMARY

Xanthomatosis has been defined as a disease, systemic in nature, characterized by the presence of tumor-like masses in the various organs, composed of cholesterol-containing xanthoma cells with varying proportions of other connective tissue elements.

There has not been found a single etiological factor for the development of the xanthomatoses, however, there is no lack of explanations. These include;the role of the liver, a pituitary factor, hormones from various organs, vitamin deficiencies, improper elimination of lipids, and imbalance between the ratio of various lipids. Irritation undoubtedly plays some role in certain of the local lipidoses.

The xanthomatoses are divided into: 1. hypercholesteremic xanthomatosis; 2. hyperlipemia with secondary eruptive xanthoma; 3. normocholesteremic xanthomatosis and; 4. Allied conditions.

Hypercholesteremic type of xanthomatosis is char-

acterized by high serum cholesterol and involvement of the skin, tendons and tendon sheaths, liver, bile ducts, gall bladder, endocardium, and blood vessels. Histologically, the foam cells are filled with cholesterol, inflammatory cells, fibroblasts, and giant cells. There is no extracellular deposits of lipid.

Hyperlipemia with secondary eruptive xanthoma is not a disease entity, but is a symptom of hyperlipemia. The serum is milky due to the great increase in neutral fat. Cholesterol and lecithin are not increased in the same proportion as the neutral fat. In hypercholesteremic xanthomatosis the serum is clear and the only lipids in abundance are cholesterol and sometimes lecithin. Histologically the lesions of secondary xanthomatosis show extracellular fat deposits, occasional foam cells and do not show granulomatous formation with giant cells.

The normocholesteremic type of xanthomatosis is characterized by normal serum cholesterol, serum not milky, and there is involvement of the skin, bones, brain, dura, pleura, lungs, lymph nodes, and spleen. In this group of diseases there is no hereditary or familial factor. The only resemblance to the hypercholesteremic type is the finding of an occasional foam cell filled with cholesterol in the lesions. This disease includes Hand-Schüller-Christian disease, Letterer-Siwe disease and eosinophilic granuloma of bone. They are diseases manifested by hyperplasia of the reticuloendothelial system and histiocytes of unknown cause. Whether they are different manifestations of the same disease, related diseases, or entirely separate diseases remains to be seen.

Gaucher disease and Niemann-Pick disease are not xanthomatoses, but are among the essential lipidoses.

Gaucher disease is rare familial systemic disorder of intracellular metabolism of reticuloendothelial cells and histiocytes, in which the cerebroside, kerasin, is accumulated in the cells. There are two types of Gaucher disease, the adult form which is an insidious and chronic disease, and the infantile form which is an acute fulminating disease. Niemann-Pick disease is a rare congenital familial disorder of the reticuloendothelial system and histiocytes as Gaucher disease. There is, in this condition, accumulation of the diamino phosphatide, sphingomyelin.

CONCLUSION

We have reviewed inthis paper the literature on xanthomatoses in an attempt to bring together and correlate the subjects under the broad title of xanthomatoses.

We have presented some newer concepts on the pathogenesis of this disease; we have been unable to contribute anything toward the etiology of the disease or to give much that will better the prognosis of the diseases. Theories on the manner of preventing hypercholesteremic changes in the body are the basis of much recent work. Treatment for the conditons presented in this paper is inadequate and discouraging.

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