Xanthoma Disseminatum

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Xanthoma disseminatum is a normolipemic disseminated xanthomatosis that tends to localize on the flexural and intertriginous surfaces, is often associated with diabetes insipidus, and appears to run a chronic benign course. Xanthomatous deposits may also be found on the mucous membranes of the mouth, pharynx and upper respiratory tract, and on the conjunctiva and cornea. Dermal infiltration by a mixture of cell types including histiocytes, xanthoma cells, numerous Touton giant cells, and inflammatory cells is typical. Lesions may persist indefinitely or involute spontaneously after many years. Respiratory obstruction due to xanthomatous involvement is a rare, serious complication and may require tracheotomy.

The disease is believed to be a granulomatous histiocytic proliferation in which lipid accumulation is secondary and is unassociated with systemic disturbances of lipid metabolism or transport. It appears to be one expression of a broad spectrum of histiocytic proliferative disorders including histiocytosis X, juvenile xanthogranuloma, histiocytoma, and reticulohistiocytoma. Usually these entities are distinct and readily categorized with their existing terminology. Observation of rare cases presenting merging clinicopathologic patterns enables one to appreciate the basic similarities underlying all these disorders.

We present a review of world literature on xanthoma disseminatum and summarize the clinicopathologic features and course in 7 Mayo Clinic cases.

The term "xanthoma disseminatum" is applied to a rare form of normolipemic mucocutaneous xanthomatosis frequently associated with diabetes insipidus. The cutaneous lesions consist of discrete disseminated red-yellow to brown papules or nodules which show a predilection for localization on the flexural surfaces and intertriginous areas such as the axillae, groin, neck, and antecubital and popliteal fossae. The lesions tend to coalesce, particularly in the axillae and groin, forming verrucous furrowed plaques. Xanthomatous deposits may also be found on the mucous membranes of the mouth, pharynx and upper respiratory tract, and on the conjunctiva and cornea. Serum-lipid values are normal.

The frequent occurrence of diabetes insipidus in patients with xanthoma disseminatum has suggested to some authors [1,2] a possible relationship to histiocytosis X of the Hand-Schüller-Christian type in which diabetes insipidus and cutaneous xanthoma are also occasionally noted. Fleischmajer,[3] however, has pointed out several arguments against such a relationship. (1) Xanthoma disseminatum usually occurs in adults, Hand-Schüller-Christian disease primarily in children. (2) Diabetes insipidus may be absent in xanthoma disseminatum, or mild and transient. (3) Bone lesions and exophthalmos are not associated with xanthoma dissemi-

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natum. (4) Involvement of the upper respiratory tract, frequently associated with xanthoma disseminatum, is not seen with Hand-Schüller-Christian disease. (5) Xanthoma disseminatum is essentially a self-limited disease with good prognosis as opposed to the usually progressive course and poor prognosis of Hand-Schüller-Christian disease. (6) The histologic picture of xanthoma disseminatum resembles that of xanthoma tuberosum and is different from that of the granuloma seen in Hand-Schüller-Christian disease.

The purpose of this study was to review the clinicopathologic features and course of xanthoma disseminatum and to attempt to determine its relationship to other xanthomatous and histiocytic proliferative disorders.

Review of Literature

The first case of xanthoma disseminatum was reported by von Gräfe [4] in 1867. The histologic and ocular findings in this case were later reviewed by Virchow [5] and Hirschberg [6] respectively. It was not until 70 years later, however, after the reports of Montgomery and Osterberg [7] in 1938 and Polano [2] in 1941, that xanthoma disseminatum was recognized as a distinct type of cutaneous xanthomatosis.

Froehlich [8] in 1951 reviewed the literature on xanthoma disseminatum and found reports of 54 cases. However, a number of the cases cited by Froehlich are unacceptable to us. In some of the early reports the information available was inadequate to warrant their inclusion as cases of xanthoma disseminatum, while other cases appeared in retrospect to represent different entities such as generalized xanthelasma [9] or pseudoxanthoma elasticum.[10,11]

Only 46 cases could be found in a review of the world literature on xanthoma disseminatum. The details of these cases have been presented elsewhere.[12] Thirty-one patients were males and 13 were females in the 44 cases in which the sex was given. The age at onset in the 44 patients ranged from 1 to 70 years, 64% noting lesions before the age of 25. In detail, the age at onset was 1 to 4 years in 7 cases, 5 to 14 years in 11, 15 to 24 in 10, 25 to 29 in 5, 30 to 39 in 2, 40 to 49 in 5, 50 to 59 in 2, and 65 and 70 years in 1 case each.

Diabetes insipidus was present in 18 cases (39%) including one probable case. In most cases it was noted either together with or after the appearance of skin lesions, but in a few it preceded the cutaneous eruption. The diabetes insipidus associated with xanthoma disseminatum is atypical in that (1) the polyuria and polydipsia are generally mild and may regress spontaneously and (2) the specific gravity of the urine may be relatively high (more than 1.003). However, necropsy evidence of xanthomatous involvement of the hypophysis and tuber cinereum in the cases of Turner and colleagues [13] and Montgomery and Osterberg [7] and the findings with the sodium chloride test (Hickey-Hare) in the patient of Mamou and colleagues [14] suggest that the diabetes insipidus is on a degenerative basis.

Xanthomatous lesions on the mucous membranes were noted in 18 patients (39%). Sites of involvement included the lips, tongue, buccal mucosa, gingiva, palate, uvula, tonsils, nasopharynx, pharynx, epiglottis, larynx, trachea, and bronchi. Symptoms of dyspnea and dysphagia were not uncommon and tracheotomy was required in 5 cases. The patient of Turner and colleagues [13] died apparently because of acute asphyxia secondary to involvement of the respiratory tract with xanthoma disseminatum; this is probably the most important complication of the disease. Nine patients had xanthomatous involvement of the conjunctiva or cornea or both.

Necropsy done in 5 of the 8 patients followed until the time of death revealed foci of internal xanthomatosis. It was difficult, however, to determine how significant these foci were in contributing to the cause of death, except in the case of Turner and colleagues.[13] In 7 additional cases the reports mentioned follow-up of the patient's condition; 5 of these patients presented evidence of partial or complete clearing of lesions while the remaining 2 had progression of

their lesions. The final outcome of the disease could not be adequately evaluated from the information available.

Mayo Clinic Cases of Xanthoma Disseminatum

Review of Mayo Clinic records revealed 6 cases in which a diagnosis of xanthoma disseminatum had been made. The clinical and laboratory data and the pathologic specimens were studied and follow-up information was obtained in these cases. In one additional case, in which histologic sections from cutaneous and muscle biopsies were on file at the Mayo Clinic, the history and follow-up data were obtained through the courtesy of Drs. E. N. Walsh and W. W. Lea, Jr. of the Scott-White Clinic. Four of these 7 cases (Cases 1 to 4) were reported previously [7,15,16] and are summarized here in order to present the results of long-term follow-up. In all 7 cases the results of routine laboratory studies, including determination of hemoglobin, leukocyte count, urinalysis, serologic tests for syphilis, and determination of fasting blood sugar and blood urea, are included only if abnormal.

CASE 1.—A 42-year-old white man came to the Mayo Clinic in June, 1927, with complaints of polyuria, polydipsia, and an eruption of about 2 years' duration. Small discrete papules were noted first in the antecubital areas; similar lesions subsequently appeared in the axillae and about the neck, scrotum, and inner canthi of the eyelids. Symptoms of polydipsia (up to 20 glasses of liquid per day) and polyuria had also been present for 2 years and had become progressively less severe.

Examination revealed an eruption consisting of small discrete yellow-brown papules 1 to 4 mm. in diameter which involved the antecubital areas, axillae, neck, eyelids, and scrotum. In the axillae and antecubital areas, lesions had formed verrucous, furrowed plaques. The urinary volume was 2,000 to 3,000 ml. per 24 hours, and the specific gravity ranged from 1.006 to 1.012. Biopsy of a cutaneous lesion in the antecubital area showed xanthoma.

In January, 1932, a marked increase in the number and size (up to 1 to 2 cm. in diameter) of the cutaneous lesions was noted. Large verrucous, pruritic, perianal plaques were present. The persistent mild diabetes insipidus did not require treatment. Xanthomatous deposits were observed on the buccal mucosa, tongue, uvula, larynx, trachea, and the outer, upper aspect of each cornea. The values for plasma lipids were: cholesterol 167 mg., cholesterol esters 119 mg., phospholipids 246 mg., fatty acids 273 mg., and total lipids 440 mg., all per 100 ml. Chemical analysis of the skin lesions revealed the total lipid content to be 8.19% of the tissue by wet weight, of which 56% was cholesterol and 44% was fatty acid. Roentgenograms of the skull and thorax were normal. A low fat diet and x-ray therapy to the region of the sella turcica and to localized areas of involvement on the neck and arms were prescribed. The perianal lesions were surgically excised.

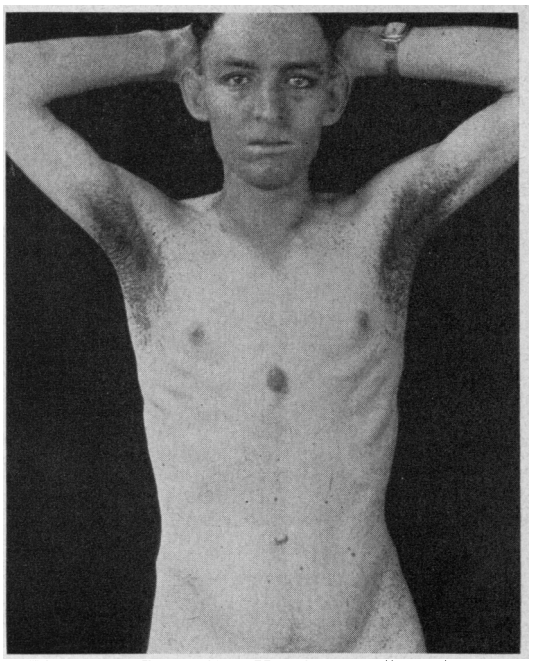


Fig. 1 (Case 2).—Xanthoma disseminatum; typical morphology and distribution of lesions.

In January, 1933, the cutaneous lesions and diabetes insipidus were essentially unchanged. The perianal lesions had recurred. In addition, the patient complained of having had severe dyspnea and ankle edema for the past 6 months. Physical findings were marked cardiomegaly, a mitral systolic murmur, rales at the base of both lungs, and hepatomegaly. The values for plasma lipids were: cholesterol 116 mg., cholesterol esters 73 mg., phospholipids 223 mg., fatty acids 260 mg., and total lipids 376 mg. Tests for liver function showed dye retention, Grade 2. The patient responded well to rest in bed and treatment with diuretics. Correspondence revealed that he subsequently had ascites and cardiac decompensation and died in February, 1935. No postmortem examination was done.

CASE 2.—A 27-year-old white man seen at the Mayo Clinic in September, 1931, had had a skin eruption for 4½ years. Small papular lesions had first appeared in the left axilla and then gradually spread to involve both axillae, the groin, neck, antecubital areas, lateral parts of the thighs, face, eyelids, back, scrotum, penis, and perianal area. Symptoms of diabetes insipidus had been present 3 years. The polydipsia and polyuria (averaging 6,000 ml. per 24 hours) were readily controlled with vasopressin. The patient also complained of hoarse-

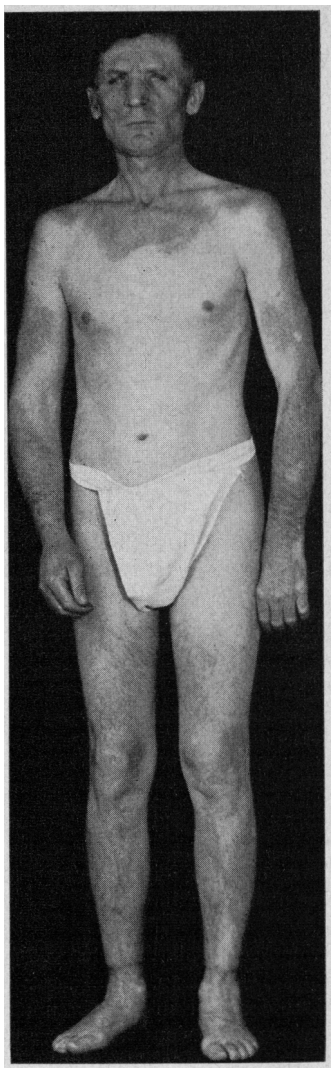


Fig. 2 (Case 3).—Xanthoma disseminatum; atypical variant showing edema, sclerosis, and "poikilodermatous" changes of involved skin.

ness, dyspnea, and a loss of 20 pounds over the last year.

Examination showed disseminated small discrete red to yellowish-brown papules and nodules with more marked concentration of lesions about the flexural and intertriginous areas, forming verrucous plaques in the axillae (Fig. 1). A pedunculated yellow-red tumor measuring 4 by 2 by 2 cm. was present over the sternal region and there were flat pale-yellow infiltrates of both eyelids. Extensive elevated yellowish xanthomatous deposits were also noted on the palate, tonsillar pillars, posterior pharyngeal wall, epiglottis, and larynx. The specific gravity of the urine ranged from 1.003 to 1.009. The values for plasma lipids were: cholesterol 172 mg., fatty acids 289 mg., and total lipids 461 mg. Chemical analysis of cutaneous lesions on 2 occasions revealed that total lipids represented 8.6% of the tissue by wet weight (40% cholesterol and 60% fatty acids) and 13.5% of tissue by weight (52% cholesterol and 48% fatty acids) respectively. Roentgenograms of the thorax, skull, spinal column, long bones, esophagus, and trachea were normal. Biopsy from lesions on the chest and in the axilla and pharynx showed xanthoma. A low fat diet was prescribed and roentgen therapy of the lesions on the face and neck was given.

The patient returned 2 months later complaining of progressive dyspnea and laryngeal stridor. The cutaneous lesions were essentially unchanged. Tracheotomy was performed. Tissue removed from the trachea showed xanthoma. The values for plasma lipids were: cholesterol 185 mg., cholesterol esters 166 mg., phospholipids 240 mg., fatty acids 380 mg., and total lipids 565 mg.

The patient died in March, 1933. Correspondence revealed that a postmortem examination done elsewhere had shown xanthomatous involvement of the larynx, trachea, bronchi, hypophysis, tuber cinereum and kidneys. The postmortem histologic sections were no longer available for review.

CASE 3.—A 42-year-old white man seen at the Mayo Clinic in May, 1935, complained of progressive hardening and discoloration of the skin. Symptoms had first been noticed 2 years before with swelling of the forearms and legs. This swelling persisted and the involved areas became increasingly indurated. In May, 1934, swelling of the cheeks and nose and a bronze-yellow discoloration of the scalp, face, neck, back, and upper part of the arms were also seen. The fingers were neither edematous nor discolored. Raynaud's phenomenon was not present, but the patient complained of numbness of the fingers and generalized weakness of 6 months' duration. There were no symptoms of diabetes insipidus.

Examination revealed that the head, neck, paravertebral region of the back, and the extensor surfaces of the forearms were covered by a diffuse erythema within which were discernible yellow-pink to orange macules that varied in extent from diffuse sheetlike involvement of the scalp, forehead and eyelids to a peppering of lesions about the neck, back, and forearms (Fig. 2). The involved skin appeared atrophic, wrinkled and "poikilodermatous." On the eyelids, chocolate-brown areas occurred with macular yellowish xanthelasma palpebrarum. The skin over the forearms, legs, and thighs was firm, "hidebound" and of a dusky purplish hue. A few scattered xanthomatous nodules were present on the anterior part of the chest. Long linear yellowish deposits were seen high on the posterior pharyngeal wall, 3 small xanthomatous nodules extending into the nasopharynx, and another was present on the left vocal cord. The values for plasma lipids were: cholesterol 124 mg.,

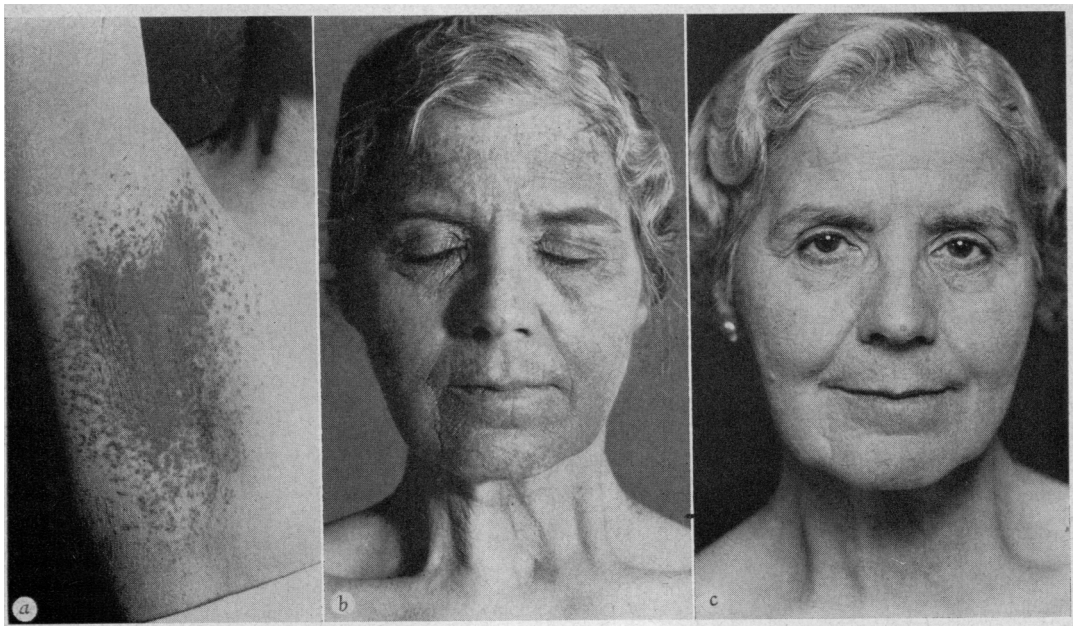


Fig. 3 (Case 4).—Xanthoma disseminatum; (*a*) xanthomatous lesions in axilla (1940); (*b*) rosacea-like erythema of face studded with numerous xanthomatous papules (1940); (*c*) spontaneous complete clearing of all lesions (1945).

fatty acids 270 mg., and total lipids 394 mg. Roentgenograms of the face, thorax, and arms were normal, and the hands showed hypertrophic changes in the terminal phalangeal joints. The results of skin biopsy of lesions on the arm, chest, and back were consistent with xanthomatosis.

In 1941, correspondence revealed that the patient had been hospitalized because of repeated episodes of fluid accumulation in the pleural spaces and abdomen. The xanthomatous lesions were unchanged; however, the patient's nose was now "large and disfigured." The value for serum cholesterol was 153 mg. The fluid accumulation apparently subsided after repeated paracentesis. In 1961, correspondence with both the patient, now aged 70, and the home dermatologist (Dr. P. K. Allen) indicated that the patient was in fairly good health. The xanthomatosis and sclerodermatous changes in the skin had not been present for more than 10 years, and his skin now appeared to show only generalized dermal atrophy.

CASE 4.—A 48-year-old white woman seen at the Mayo Clinic in June, 1936, had had a papular skin eruption for 1 year. Papules had first appeared in both axillae and then had spread to involve the eyelids, groin, and thighs. Six months later she developed symptoms of diabetes insipidus, which were well controlled with vasopressin and amidopyrine.

Examination revealed discrete red-yellow to brown papules 1 to 3 mm. in diameter about the eyelids and thighs and in the groin and axillae (Fig. 3*a*), where the lesions were more coalescent. There was also a diffuse erythema of the face. Otherwise, physical and neurologic findings were negative. The values for plasma lipids obtained on several occasions are given in Table 1. The specific gravity of the urine ranged from 1.002 to 1.009. Roentgenograms of the thorax and skull were normal.

In 1937 the number of lesions about the thighs, groin, and axillae had increased, and scattered

TABLE 1.—*Values for Plasma Lipids (Milligrams per 100 Ml.)*

	Date and Value							
	6/36	3/37	10/37	1938	1940	1941	1945	1961
Cholesterol	214	231	238	235	238	228	260	326
Cholesterol esters				174	194		159	
Phospholipids		297	356	225	212	214	235	
Fatty acids	203	405	542	438	304	278	214	
Total lipids	516	636	780	673	552	506	474	

lesions were also present on the abdomen. The pruritic erythema involving the rosacea area of the face was marked and within this area were numerous miliary xanthomatous papules (Fig. 3*b*). Xanthomatous deposits were also noted on the buccal mucosa and the floor of the mouth and in the larynx. The value for serum bilirubin was normal, and there was no retention of dye with the sulfobromophthalein test. Biopsy of a lesion in the axilla showed xanthoma. A low fat diet was prescribed.

In 1941 the patient's skin showed marked improvement with flattening of lesions in almost all areas of involvement. The xanthomatous papules on the face had resolved, leaving only mild erythema. The symptoms of diabetes insipidus were subsiding.

In January, 1945, the patient was completely free of skin lesions (Fig. 3*c*). Symptoms of diabetes insipidus had almost completely disappeared. Correspondence with the patient, now aged 73, and her home physician revealed that she was in good health with no skin lesions or diabetes insipidus. A recent examination at home had showed moderate hypertension (blood pressure 160/100). Roentgenograms showed ectasia and calcification of the ascending and descending aorta. Evidence of left axis deviation was noted on the electrocardiogram. The value for serum cholesterol was 326 mg.

CASE 5.—A 28-year-old white man seen at the Mayo Clinic in December, 1950, had had a papular skin eruption for 2 years. Lesions had first appeared in both axillae and later had been noted in the antecubital areas and groin, on the chin and about the lateral aspects of the neck. The patient also complained of a tendency to drowsiness, present for 6 months, which had become so severe that he was afraid to drive his car and required 10 mg. of amphetamine every 4 hours to stay awake during the afternoon. There were no symptoms of diabetes insipidus and no family history of narcolepsy.

Examination revealed numerous discrete pea-sized yellow to brown papular lesions scattered about the chin, the lateral aspects of the neck, and in the axillae and groin, with some slight coalescence of papules in the axillae. There was one small questionable xanthomatous deposit in the nasopharynx. Otherwise, physical and neurologic findings were negative. Values for plasma lipids were: cholesterol 117 mg., cholesterol esters 78 mg., phospholipids 170 mg., fatty acids 251 mg., and total lipids 368 mg. Roentgenograms of the skull and thorax and an electroencephalogram were normal. Examination of the cerebrospinal fluid revealed no significant abnormality. The findings on biopsy of a skin lesion in the axilla were consistent with xanthoma. Diagnoses of narcolepsy and xanthoma disseminatum were made and the patient was dismissed without treatment.

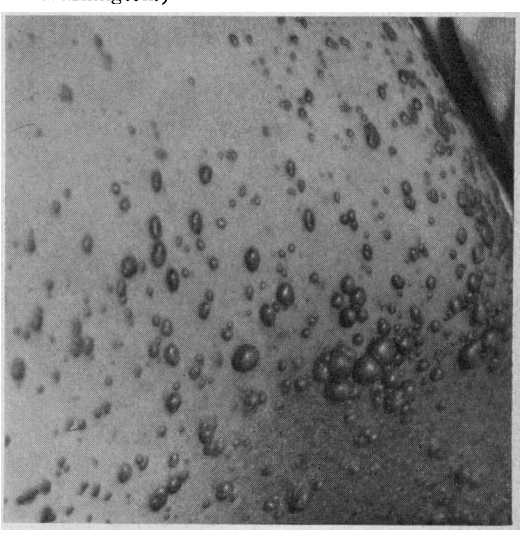
Correspondence in March, 1951, revealed that ultracentrifuge studies of his blood, done elsewhere, had shown no abnormality of the blood-lipid pattern. The home physician later reported that the patient died in a plane crash in 1956. At the time of death the symptoms of narcolepsy had subsided spontaneously to a considerable degree; however, the skin lesions were numerous and had continued to appear. Apparently postmortem examination was not done.

CASE 6.—A 22-year-old white woman seen at the Mayo Clinic in July, 1959, had had a cutaneous eruption for 4 months. Papular lesions first appeared in the right axilla with similar lesions soon involving the left axilla, trunk, hips, inner part of the thighs, arms, back, face, neck, and eyelids. The lesions showed some tendency to coalesce, especially in the intertriginous areas. The patient had gained 20 pounds in the last 2 months and had noticed some dependent edema of the ankles. She had no symptoms of diabetes insipidus.

Physical findings were essentially normal except for the skin lesions. No lesions were noted on the mucous membranes. Values for plasma lipids were: cholesterol 168 mg., cholesterol esters 124 mg., phospholipids 193 mg., fatty acids 332 mg., and total lipids 500 mg. The results of serum-protein electrophoresis were normal. A roentgenogram of the thorax did not show any abnormality. A biopsy specimen from a lesion in the axilla and a previous biopsy specimen obtained elsewhere 2 months before demonstrated an infiltrate of histiocytes.

Correspondence with the patient and her physician (Dr. J. W. Ormsby) in July, 1961, revealed that she was in good health. Her skin lesions were persistent and some had enlarged to nodular size (Fig. 4), but apparently no new lesions had appeared since the fall of 1959. Recent roentgeno-

Fig. 4 (Case 6).—Papular and nodular lesions of xanthoma disseminatum on inner aspect of left thigh. (Courtesy of Dr. J. W. Ormsby, University of Washington.)



grams of the skull, pelvis, and femurs had shown no abnormalities. The value for serum cholesterol was said to be within normal limits, and a urine-concentration test had given normal results.

CASE 7.—A 67-year-old white woman was seen at the Scott-White Clinic in 1947 for a cutaneous eruption that had been present 2 years. Lesions consisted of yellow-brown papules and nodules involving the flexural areas, forearms, shoulders, scleral conjunctivae and vocal cords. These lesions increased slowly in number and size, and when the patient was seen again, in 1949, deeper tumors had appeared, apparently involving the muscles of the forearm. The patient also complained of increasing hoarseness. Biopsy of skin and muscle lesions showed xanthoma. The sections and blocks from these biopsies were reviewed at the Mayo Clinic and are now on file there.

In 1950 the patient experienced an episode of fever and pain in the shoulder and flank. Roentgenograms of the ribs, shoulder and skull revealed no abnormality. Urinalysis showed Bence Jones proteinuria on 3 occasions, and the γ-globulin fraction of the serum proteins was noted to be increased; however, she was not seriously ill, and there were no other findings to suggest multiple myeloma. Values for serum cholesterol determined on a number of occasions ranged from 89 to 166 mg. Symptoms of diabetes insipidus had never been present.

Follow-up correspondence revealed that the patient died in June, 1955, at age 75, apparently as a result of a cerebral vascular accident. No information could be obtained as to the condition of the skin lesions at the time of death. Postmortem examination was not done.

Histopathologic Findings in Cases 1 to 7.—Single or multiple biopsy specimens of skin lesions were available from all 7 patients. In addition, mucosal lesions in the pharynx and trachea had been subjected to biopsy in Case 2; also postmortem examination had been done elsewhere in this case, but neither complete records nor the histologic sections from this examination were available.

Biopsy sections from cutaneous lesions in 6 of the 7 patients (Cases 1, 2, 4, 5, 6 and 7) appeared similar. Biopsy sections in Case 3 were atypical and will be discussed later. The predominant histologic feature in biopsies from the 6 patients was dermal infiltration by large mature-appearing histiocytic cells with abundant eosinophilic cytoplasm and with large pale vesicular nuclei containing prominent nucleoli. Accompanying the histiocytes was an inflammatory-cell infiltrate consisting chiefly of lymphocytes, polymorphonuclear leukocytes and occasional eosinophils. The overlying epidermis usually showed some flattening of the rete ridges and varying degrees of increased pigmentation in the basal layer. The degree of lipid accumulation within histiocytes and the number of xanthoma and Touton giant cells appeared to vary with the duration of the lesions. Biopsy of a 2-month-old axillary lesion in Patient 6 showed a dermal infiltrate consisting entirely of large nonfoamy histiocytes, some of which were spindle shaped, and inflammatory cells. The picture was similar to that of histiocytoma cutis (Fig. 5). No xanthoma cells or giant cells were present. Sudan IV and iron stains gave negative results in this specimen. A repeat biopsy 2 months later showed a similar picture except that some of the histiocytic cells in the deeper portions of the lesion now appeared to have vacuolated foamy cytoplasm. Sudan IV stain showed these vacuoles to be lipid droplets. Xanthoma cells and Touton giant cells were still absent, and the iron stain gave negative results.

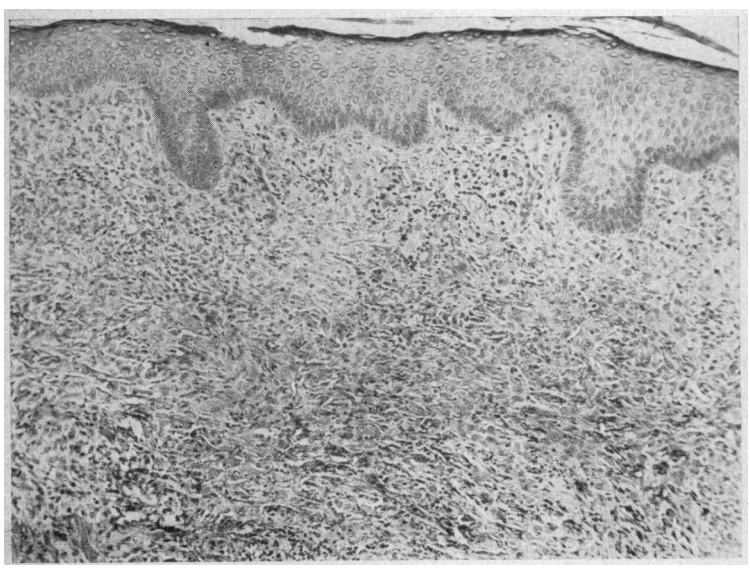


Fig. 5 (Case 6).—Skin biopsy specimen from axilla (disease of 2 months' duration). Dermal infiltrate consists of large nonfoamy histiocytes, spindle-shaped cells, and inflammatory cells (hematoxylin and eosin; × 100). Staining for lipid and iron gave negative results in this specimen.

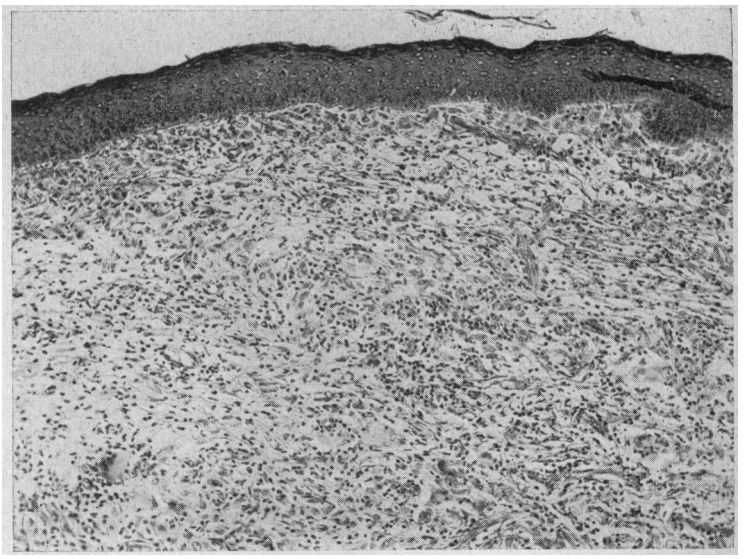


Fig. 6 (Case 5).—Skin biopsy specimen from axilla. Dermal infiltrate consists of foamy histiocytes, foci of xanthoma cells, a few multinucleated giant cells, and inflammatory cells (hematoxylin and eosin; × 100). Staining for lipid and iron gave positive results.

Patient 5 had had skin lesions for 2 years but they were not numerous and had remained relatively small and discrete. Histologic sections of an axillary lesion of longer duration than in Patient 6 showed dermal infiltration by a mixture of cell types. The predominant cells were large histiocytes with eosinophilic cytoplasm which appeared foamy. There were also foci of typical xanthoma cells. An accompanying inflammatory-cell infiltrate and a few multinucleated histiocytes, but no Touton giant cells, were seen (Fig. 6). Both the Sudan IV and iron stains gave positive results, with most of the iron appearing just beneath the epidermis in the papillary layer of the dermis.

In Cases 1, 2, 4, and 7, clinical involvement was more extensive and the histologic picture was considered typical of xanthoma disseminatum. Biopsy sections from these patients revealed similar dermal infiltrates consisting of a mixture of cell types with (1) large eosinophilic histiocytes, some with foamy cytoplasm, (2) foci of lipid-laden xanthoma cells, (3) numerous Touton giant cells and (4) occasional giant cells of the foreign-body type, and similar inflammatory-cell infiltrates consisting predominantly of lymphocytes and polymorphonuclear leukocytes (Fig. 7). In patient 7 the infiltrate extended down into the connective-tissue septa of skeletal muscle underlying the skin lesions. Patient 2 had a submucosal infiltrate in the lesions of the pharynx and trachea that was similar to that present in the cutaneous lesions. Sudan IV staining gave positive results in all 4 patients. Droplets of sudanophilic material were noted within the cytoplasm of histiocytes, in xanthoma cells, and in Touton giant

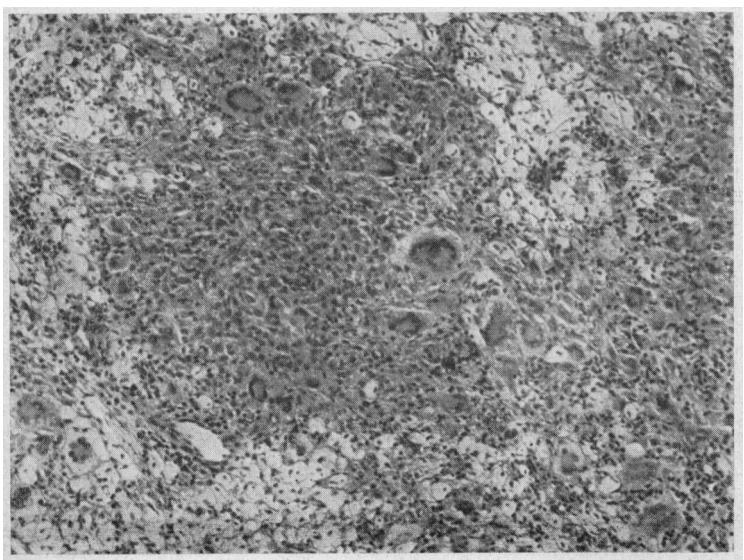


Fig. 7 (Case 2).—Skin biopsy specimen from axilla. Typical histologic picture of xanthoma disseminatum with a mixture of cell types including histiocytes, foam cells, numerous Touton giant cells, and inflammatory cells (hematoxylin and eosin; × 100).

TABLE 2.—*Course of Xanthoma Disseminatum*

Case	Age		Duration, Yr.		Course
	Onset	Present	Lesions	Follow-Up	
					Patients Still Living
3	40	70	20	30	Free of xanthomatous lesions and sclerodermatous skin changes for 10 yr.; only persistent generalized dermal atrophy remaining; now "in fairly good health"; no recent lab. data; diabetes insipidus never present
4	47	73	10	26	Free of skin lesions and diabetes insipidus for 16 yr.; no residua; recent exam.: moderate hypertension & slight increase of serum cholesterol (326 mg.)
6	22	24	2	2	Skin lesions persistent but apparently not progressive; general health excellent; serum cholesterol normal; diabetes insipidus not present
					Deceased Patients
1	40	50	10		Skin involvement slowly progressive; diabetes insipidus appeared improving; death due to cardiac decompensation (?); no necropsy
2	23	29	6		Skin and mucous-membrane involvement slowly progressive; tracheotomy; diabetes insipidus remained mild; necropsy: xanthomatosis of larynx, trachea, bronchi, hypophysis, tuber cinereum, kidneys, & skin; cause of death unknown
5	26	34	8		Skin lesions slowly progressive; narcolepsy apparently resolving spontaneously; death accidental; no necropsy
7	67	75	8		Skin lesions present at death but extent unknown; death apparently due to cerebral vascular accidents; no necropsy; diabetes insipidus never present

cells. Some biopsies also showed the presence of lipid which appeared to be extracellular. Stains for iron also gave positive results in these patients. The iron was found within histiocytes and giant cells and was located within the papillary dermis in 2 patients (Cases 1 and 4), while in 2 (Cases 2 and 7) it was distributed more diffusely throughout the lesion and also appeared both within and outside of histiocytes.

Case 3 presented atypical features both clinically and histologically. Biopsies from lesions on the arm, chest, and back showed a dermal infiltrate consisting entirely of large lipid-laden xanthoma cells, scattered inflammatory cells, and a rare giant cell of the foreign-body type. The eosinophilic histiocytes and numerous Touton giant cells noted in other cases were absent. Increased proliferation of fibrous tissue and thinning of the epidermis were noted in all 3 biopsy specimens in Case 3. The fibrosis was most evident in the skin of the forearm, which showed a sparse foam-cell infiltrate located about the dermal blood vessels only. In contrast, biopsy of lesions of the back revealed little fibrosis and a dense foam-cell infiltrate occupying the entire upper third of the corium. Sudan IV stains gave positive results and stains for iron and for acid-fast organisms gave negative results in all 3 biopsy specimens. This case is best interpreted as an atypical variant of xanthoma disseminatum in which the lesions exhibit an unusual tendency toward proliferation of fibrous tissue.

Comment on Cases 1 to 7.—Four patients were males and 3 were females. Age at onset of the disease ranged from 22 to 67 years (average 37 years). At the time of follow-up, 4 patients were dead and 3 were still living. The findings at the time of follow-up are summarized in Table 2.

The duration of lesions in 2 patients (Cases 3 and 4) still living and now clear of the disease was 20 and 10 years respectively. The duration of lesions at the time of death in 4 patients ranged from 6 to 10 years and averaged 8 years. Although lesions of xanthoma disseminatum were present in all 4 patients at the time of death, the cause of death did not appear to be related to xanthomatous involvement, except perhaps in Patient 2, in whom there was postmortem evidence of extensive involvement of the larynx, trachea, and bronchi.

Thus, on the basis of these 7 cases, xanthoma disseminatum appears to be a chronic, essentially benign disease of adults. The lesions may persist indefinitely or involute spontaneously after many years. There does not seem to be any correlation between the extent of skin or nervous-system involvement as with diabetic insipidus at the time the patient is seen and the eventual outcome of the disease. The presence of extensive xanthomata on the mucous membranes of the respiratory tract may cause obstructive symptoms, and this should be the physician's principal concern. There is no effective treatment for xanthoma disseminatum. The diabetes insipidus is usually controlled with posterior pituitary extracts.

Pathogenesis and Relationships

Is xanthoma disseminatum primarily a systemic disturbance of lipid metabolism or transport, or is it an inflammatory, granulomatous, proliferative disorder with subsequent accumulation of lipids? The view that it is a primary systemic disturbance of lipid metabolism or transport seems improbable since the values for serum lipids are usually normal. Studies of alimentary hyperlipemia reveal that patients with xanthoma disseminatum handle ingested fats normally [17,18] and the disease does not respond to treatment with a low fat diet. Furthermore, ultracentrifuge studies of the blood of one patient (our Case 5) revealed no detectable lipid abnormalities. In several reported cases however, there was moderate increase of either plasma cholesterol (case of Spillmann and Watrin [19] and our Case 4) or total lipids.[13,20,21] The increased values for lipids in these few cases are overshadowed by the normal values observed in most cases. Available evidence suggests that xanthoma disseminatum is not primarily a systemic disturbance of lipid metabolism or transport.

The histologic appearance of the lesions of xanthoma disseminatum suggests that the disease is basically a reactive, histiocytic proliferation in which lipid is accumulated as a secondary phenomenon. In lesions of recent onset the proliferation of large histiocytic cells dominates the picture, with little or no lipid accumulation and no xanthoma cells or Touton-cell formation (our Case 6 and case of Gottron).[22] As the disease progresses, lipidization of histiocytes increases with "xanthoma"-cell formation, and finally the typical histologic picture of xanthoma disseminatum is seen with a mixture of histiocytes, xanthoma cells, inflammatory cells, and numerous Touton giant cells.

The above findings suggest a relationship between the phases of development of xanthoma disseminatum and the 4 stages of development of lesions of histiocytosis X as described by Engelbreth-Holm and associates [23] (namely hyperplastic-proliferative, granulomatous, xanthomatous, and fibrous stages). However, there are differences as well as similarities that are worthy of comment. These differences include the following: (1) A stage corresponding to that of eosinophilic granuloma is absent in lesions of xanthoma disseminatum. Eosinophils when present are usually sparse and do not appear in nests or clusters. (2) Histiocytes in the lesions of xanthoma disseminatum have a benign appearance. The pleomorphism and increased mitotic activity usually associated with the cells of histiocytosis X are not noted. Early lesions of xanthoma disseminatum, prior to lipid accumulation, resemble those of histiocytoma cutis histologically. (3) The foam cells and numerous Touton giant cells seen in xanthoma disseminatum provide a more strikingly xanthomatous appearance than is seen in lesions of Hand-Schüller-Christian disease that have accumulated lipid. This very xanthomatous appearance has led others [7] to state that the histology of xanthoma disseminatum is identical with that of xanthoma tuberosum. Xanthoma tuberosum, however, does not usually show the variety of cell types, particularly the large histiocytes and numerous Touton giant cells that are typical of xanthoma disseminatum. We believe that typical xanthoma disseminatum can be distinguished from both xanthoma tuberosum and histiocytosis X of the Hand-Schüller-Christian type on a histologic basis. However, the histologic criteria for distinguishing xanthoma disseminatum from juvenile xanthogranuloma or (in early lesions) from histiocytoma are more vague and at times such distinction may be impossible.

It is apparent that the relationship of xanthoma disseminatum to histiocytosis X, juvenile xanthogranuloma, and histiocytoma cutis bears further investigation. It should be noted that several cases accepted as xanthoma disseminatum in the review of literature also showed atypical features suggesting a relationship to other histiocytic proliferative disorders such as histiocytosis X, juvenile xanthogranuloma, histiocytoma, and reticulohistiocytoma. These relationships will be considered individually.

Relationship of Xanthoma Disseminatum and Histiocytosis X.—Histiocytosis X (reticuloendotheliosis, eosinophilic xanthomatous granuloma, reticulogranuloma, and so forth) has been the subject of several recent reviews [3,24] covering the early literature and the evolution of the present concept of the disease as including the entities previously described as Letterer-Siwe disease, Hand-Schüller-Christian disease, and eosinophilic granuloma. In this paper the term "histiocytosis X" refers to the entire group.

Various cutaneous lesions occur with the various types of histiocytosis X. These include (1) a diffuse papular or scaling "seborrheic" eruption, (2) a petechial purpuric eruption, (3) granulomatous and ulcerative lesions, (4) xanthomatous lesions and (5) bronzing of the skin. Lesions are almost always present in Letterer-Siwe disease and are frequently purpuric or papular. With eosinophilic granuloma, cutaneous involvement is only rarely seen and may appear as ulcerative granulomatous lesions involving mucocutaneous areas. Skin lesions occur in about one-third of patients with Hand-Schüller-Christian disease. The papular and scaling "seborrheic" lesions seem to be the most frequent cutaneous manifestation of Hand-Schüller-Christian disease, and when such lesions are widespread they have been referred to erroneously as xanthoma disseminatum by some authors. It should be pointed out that xanthomatous lesions occur infrequently in Hand-Schüller-Christian disease (and extremely rarely in Letterer-Siwe disease and eosinophilic granuloma). Thannhauser [1] has put unwarranted stress on the cutaneous xanthoma occurring in Hand-Schüller-Christian disease by considering the lesions of xanthoma disseminatum as typical cutaneous manifestations of Hand-Schüller-Christian and using as illustrations Mayo Clinic cases of xanthoma disseminatum (Cases 1 and 4). Actually, review of the literature reveals only one case [22] that appears acceptable as typical Hand-Schüller-Christian disease associated with typical xanthoma disseminatum.

This exceptional case is significant in that it provides the "missing link" between typical Hand-Schüller-Christian disease and typical xanthoma disseminatum and points out the underlying relationship of these entities.

Relationship of Xanthoma Disseminatum and Juvenile Xanthogranuloma.—Lesions of juvenile xanthogranuloma (nevoxanthoendothelioma) consist of single or multiple discrete yellow-orange xanthomatous papules or nodules usually appearing on the scalp, face, upper part of the trunk, and upper extremities and rarely involving the mucous membranes. The lesions most frequently develop within the first few months of life but have also been observed at birth and in older children. The children remain entirely well, and the lesions generally involute without residue within a few years. The values for serum lipids are always normal. Bluefarb [25] and Fleischmajer and Hyman [26] have recently reviewed the subject of juvenile xanthogranuloma.

There are several case reports of juvenile xanthogranuloma with evidence of systemic involvement. Most commonly, extracutaneous lesions involve the eye (9 cases).[27] These patients generally present with spontaneous hemorrhage into the anterior chamber and show xanthogranulomatous infiltration of the bulbar structures (iris, ciliary body, and so forth). Lamb and Lain [28] in 1937 reported on a 3-month-old child with extensive "nevoxanthoendothelioma" over the scalp and scattered lesions over the back, chest, buttocks and vulva. At age 14 months, numerous nodular lesions appeared in both lung fields, and the liver was enlarged. The lung lesions later resolved, and at age 5 years the child was reported to be in good health. The value for serum cholesterol was normal. Bone lesions, exophthalmos, and diabetes insipidus were never present. Histologic examination of skin lesions at various stages in their development showed progression through histiocytic, xanthomatous, and finally fibrotic phases. The visceral lesions were not subjected to biopsy.

Helwig and Hackney [29] in 1954 reviewed 53 cases of juvenile xanthogranuloma including one case in which multiple cutaneous

TABLE 3.—*Comparison of Xanthoma Disseminatum and Juvenile Xanthogranuloma*

Condition	Xanthoma Disseminatum	Juvenile Xanthogranuloma
Age at onset	Usually adolescents or young adults	Usually in first months of life
No. and distribution of lesions	Numerous lesions involving flexural & intertriginous areas, frequently coalescent	Few lesions scattered over scalp, face, neck, trunk and upper extremities, mostly discrete
Mucous-membrane lesions	Frequent; involving oral mucosa, pharynx, & respiratory tract	Rare; involving oral and genital mucous membranes
Eye lesions	Frequent; involving epibulbar structures (conjunctiva and cornea)	Rare; involving bulbar structures (iris, ciliary body)
Systemic involvement	Diabetes insipidus frequent; other foci found more rarely (e.g., kidney, stomach, marrow, pons)	Unassociated with diabetes insipidus; visceral foci found very rarely (e.g., in lung, liver, testis)
Prognosis	? Chronic course with clearing of lesions in some cases; eventual outcome difficult to predict	Excellent, with lesions clearing without residua in most cases
Relation to Hand-Schüller-Christian disease	Typical xanthoma disseminatum and typical Hand-Schüller-Christian disease associated in only 1 case in world literature	Several reported cases of typical Hand-Schüller-Christian disease with cutaneous lesions identical with juvenile xanthogranuloma

lesions were noted over the entire body and in which lesions were found in the lung and testis at necropsy. The cause of death was not mentioned. The authors expressed the opinion that juvenile xanthogranuloma is not related to histiocytosis X.

Nödl [30] in 1959 reported on a child who showed several large nodular lesions of nevoxanthoendothelioma involving the trunk and extremities and a similar lesion involving the testis.

Comparison of the gross features of xanthoma disseminatum and juvenile xanthogranuloma reveals the differences listed in Table 3. Comparison of histologic criteria for the separation of these entities reveals very few differences. Both lesions consist essentially of a mixture of cell types including large, relatively mature histiocytes, foam cells, numerous multinucleated giant cells, and inflammatory cells, mainly lymphocytes and polymorphonuclear leukocytes. In xanthoma disseminatum the giant cells are predominately of the Touton type whereas in juvenile xanthogranuloma they are more frequently of the foreign-body type (so-called endothelial giant cells). It should be noted, however, that the histologic features of juvenile xanthogranuloma may vary considerably. At times lesions may show numerous Touton giant cells and appear very similar to those of xanthoma disseminatum, while at other times there may be marked predominance of xanthoma cells with very few histiocytes or giant cells so that the only diagnosis that can be made is "consistent with xanthoma."

The similarities between these 2 entities have led several authors [1,31] to use the terms "xanthoma disseminatum" and "juvenile xanthogranuloma (nevoxanthoendothelioma)" synonymously. The rare association of both types of lesions with Hand-Schüller-Christian disease has prompted Thannhauser [1] to consider both xanthoma disseminatum and juvenile xanthogranuloma as "formes frustes" or mild "monosymptomatic" types of Hand-Schüller-Christian.

Some of the clinical confusion between these entities is understandable, particularly since occasionally there is extensive cutaneous involvement with lesions of juvenile xanthogranuloma, while xanthoma disseminatum may at times appear with few skin lesions. It was previously mentioned that some of the early case reports of xanthoma disseminatum might be interpreted as representing juvenile xanthogranuloma. Proof that this dilemma of classification is still with us is offered in the recent report by Cogan and colleagues.[27]

This patient, a 5-year-old white girl, was reported as the first case of "epibulbar nevoxanthoendothelioma." She had had photophobia, blepharospasm, and small vascularized yellowish nodules involving the limbus of both eyes and extending out onto the cornea, present for 18 months. In addition, she had several small erythematous papules

on the eyelids and numerous (50 to 100) discrete yellowish papules in both axillae. Physical findings were otherwise essentially normal. The iris, media, and fundi were normal. The value for serum cholesterol was 158 mg. The epibulbar lesions were partially excised. Histologic examination of this tissue revealed an infiltrate consisting of foam cells and scattered foreign-body giant cells involving all layers of the cornea. In addition, proliferation of connective tissue and blood vessels and an inflammatory-cell infiltrate consisting of lymphocytes and polymorphonuclear leukocytes were noted. Biopsy of a skin lesion in the axillae showed dermal invasion by histiocytic cells, some of which were multinucleated, and an accompanying inflammatory-cell infiltrate. No Touton giant cells or foam cells were present, and stains for fat gave negative results.

Although such "merging" cases point to a basic relationship between these diseases, in most instances xanthoma disseminatum and juvenile xanthogranuloma are obviously separable and merit distinction from one another and from histiocytosis X. The possibility of systemic lesions of juvenile xanthogranuloma and the rare association of this entity with Hand-Schüller-Christian disease should, however, always be kept in mind by the clinician.

Relationship of Xanthoma Disseminatum to "Xanthosiderohistiocytosis" and Histiocytoma.—Halprin and Lorincz [32] in 1960 reported an interesting and unusual case of "xanthosiderohistiocytosis (xanthoma disseminatum)."

This patient, a 45-year-old white man, presented a bizarre skin eruption of 5 years' duration. Lesions were present over the face, chest, and back and consisted of irregular brownish-green, firm, infiltrated plaques, some of which (on the face) showed yellowish borders. Over the thighs and abdomen were less well-defined nodular purplish dermal infiltrates, and there was wasting of the skeletal muscle underlying skin lesions, particularly about the shoulders and thighs. Xanthomatous deposits were present on the conjunctiva of both eyes. The patient complained of weakness, photophobia, anorexia, impotence, loss of 40 pounds, and persistent edema of the ankles. He had had moderate mental disturbance affecting memory and personality for about 1 year. He did not have any lesions of the mucous membrane.

Values for serum cholesterol ranged from 56 to 115 mg.; the value for phospholipids was 107.5 mg. and for total lipids 418 mg. A roentgenographic survey of the bones did not show any abnormality. Liver-function studies gave normal results. Biopsy of a skin lesion disclosed a diffuse dermal infiltrate consisting of large histiocytic cells with foamy cytoplasm and small, darkly staining, centrally placed nuclei. There were a few multinucleated giant cells, an occasional Touton giant cell, and an increased proliferation of fibrous tissue. The subcutaneous tissue and underlying muscle fibers were diffusely infiltrated by small foci of similar cells. The cytoplasm of the histiocytes contained granules that stained for iron. Bone-marrow aspiration showed similar histiocytic cellular deposits intermingled with normal marrow elements. The patient died in 1959. The cause of death was not known. Postmortem examination was not done.

Several features of this case are atypical for xanthoma disseminatum. These include distribution of lesions, edema and firmness of skin in involved areas, and involvement of the skeletal muscle. In this respect, "xanthosiderohistiocytosis" seems similar to 2 other atypical cases of xanthoma disseminatum: (1) the case of Frank and Weidman,[33] with similar distribution of lesions, sclerodermoid changes, and skeletal-muscle involvement, and (2) Mayo Clinic Case 3, with similar distribution, edema, and poikiloscleroderma-like changes.

Halprin and Lorincz [32] stressed the presence of iron in biopsy specimens from their patient. Our findings also suggest that iron is frequently present in lesions of xanthoma disseminatum. However, in Case 6 (a very early lesion) and in Case 3, staining for iron gave negative results. The absence of iron in all of the several biopsy specimens available in Case 3 was surprising in that this

case appeared to be atypical, with some features akin to Halprin and Lorincz's case. Since staining for iron does not give positive results in all cases of xanthoma disseminatum, we believe that creation of the new term "xanthosiderohistiocytosis" is unwarranted. Until there is better understanding of unusual cases such as that of Halprin and Lorincz and that of Frank and Weidman they are most logically categorized as variants of xanthoma disseminatum.

Halprin and Lorincz [32] also pointed out that the initial lesions in their patient were clinically identical with histiocytoma, and they suggested a possible relationship between xanthoma disseminatum and histiocytoma cutis. The lesion of histiocytoma cutis (nodular subepidermal fibrosis, dermatofibroma, sclerosing hemangioma) is a chronic, round to oval, intradermal papule or nodule which may be seen on any part of the body but frequently involves the extremities. The color varies from pale yellow through shades of red and brown to blue black. Lesions usually grow slowly up to about 2 cm. in diameter and then remain stationary thereafter. Most commonly, one or several lesions are present, but on rare occasions widespread involvement may occur.[34] The subject of histiocytoma was reviewed recently by Bluefarb.[25] Multiple disseminated histiocytomas apparently are extremely infrequent. Because of their possible relation to xanthoma disseminatum the following case is reported.

A 58-year-old white man came to the Mayo Clinic in March, 1959, complaining of a skin eruption of 6 months' duration. Lesions consisted of discrete, firm, red-brown nodules 3 to 7 mm. in diameter that involved the nasal alae, sides of the neck, axillary folds, pubic area, and the penis and scrotum. About 40 lesions were present. Physical and laboratory findings were otherwise negative. Correspondence in 1961 from the patient's home physician revealed that there now were "hundreds" of pea-sized, pink-red nodules involving the areas previously mentioned and also the chest, back, abdomen, and extremities. The patient had remained in good health. Review of skin-biopsy specimens taken in 1959 and 1961 revealed histiocytoma cutis.

The similarities between the histologic appearance of early lesions of xanthoma disseminatum and those of histiocytoma have been mentioned previously, and it can be seen from the above case that at times multiple histiocytoma may occur with a pattern of distribution similar to that of xanthoma disseminatum. The presence of lesions of histiocytoma as the initial ones in the case of Halprin and Lorincz [32] provides another unusual example of overlapping clinical features suggesting a relationship between 2 entities usually considered distinct. This case seems to link xanthoma disseminatum and multiple histiocytoma in the same manner that the case of Gottron [22] links xanthoma disseminatum and histiocytosis X. These findings suggest that xanthoma disseminatum represents one segment of a broad spectrum of related histiocytic responses occurring in the skin, which also includes histiocytosis X, juvenile xanthogranuloma, histiocytoma, and possibly reticulohistiocytoma. Observation of rare cases with merging clinicopathologic features enables one to appreciate the basic similarities underlying this spectrum of disease.

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