Studies in xanthoma

Biochemistry and Pathogenesis *

by

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(With 5 text charts)

The study of lipidoses, especially of skin lipidoses, is now following new lines, owing to the enhanced technique of physiological chemistry. Qualitative and quantitative determinations carried out in humours and tissues are allowing more exact classifications of facts which have been observed for a long time past, but are not well known as yet. In the present paper, we advance some interpretations, mainly deduced from the tests and dosages effected in two cases as well as from certain important verifications, notably: excretion of large quantities of cholesterol through urine without renal lesion, occurrence of reactions of tissular hypersensitivity to cholesterol, etc.

I. DOCUMENTS REGARDING TWO CASES

Case 1. — Circumscribed nodular xanthelasma: P. C. V., 36 years of age, white complexion, Brazilian, military man, married. Family history: — Parents dead, cause of death unknown. In the family there is no case analogous to his. Personal history: — Patient alleges no disease in infancy or adolescence. He married at the age of 20 years. His wife died, when she was 26 years old, from «tuberculosis». They had six children, of whom 2 died from «tuberculosis», at the age of 4 and 7 years respectively; a third one died at the age of 1 year, from a cause which had not been determined. At the age of 22 years, patient had an ulcerous lesion on the glans which cicatrized under the action of topical treatment, and presented no more important clinical sequelae. At the age of 30 years, he married again, this time a healthy woman. Past history of the present disease: — About one year and a half ago, on the left elbow the first lesions of the present disease appeared, followed, at intervals, by eruption of other elements on the other elbow

* Work carried out in the Dermatologic Clinic of Faculty of Medicine, in charge of Prof. E. Rabello.
and on the knees. Lately, an identical lesion appeared on the lower lip. Description of the lesions and their localisation follows: Small tubercles, strictly located at the level of the elbows and knees, appearing on adjoining spots of the same region, so as to form a confluent tuberous band resembling a leproma (on the left elbow). There is a flat infiltration on the cutaneo-mucous border of the lower lip; we must mention the fact that the remaining buccal mucosa and other visible mucosae present nothing abnormal in their appearance, consistency, or colour. The infiltration existing on the lip gives the involved portion of mucosa a yellowish tonality. The surface of the patch is smooth and finely plicated, its centre being slightly depressed. Apart from the regions mentioned, the surface of the integument appears normal, with the exception of the colour, which is a peculiar bronzed-brown. The tubercles are dark yellow (saffron yellow) and rest directly on normal skin, any inflammatory reaction or infiltration not being observed. They are resistent, but not indurated, slightly painful at pressure. Profound palpation of the muscular masses of the limbs and exploration of the joints do not reveal the existence of peritendinous or periarticular infiltrations. There is no xanthelasma on the eyelids. Examinations:—The other clinical examinations revealed nothing abnormal with regard to the various systems and apparatus.

Case II.—Diffused micropapulous xanthelasma: C. M., 46 years of age, white complexion, Portuguese, single, commercial clerk. Family history:—Father died at the age of 75 years, from «heart disease». Mother died at the age of 68 years from «cancer». In the family there is no case analogous to his. Personal history:—In infancy, measles, chicken-pox. At the age of 17 years, venereal lesion which cicatrizened without any clinical sequel. At the age of 30, patient was afflicted with an acute attack of gonorrhea. At the age of 31, grippe (pandemia of 1918). Patient informs that some time afterwards he suffered from a rheumatoid affection with swelling of the knees, which phenomenon ceased of itself. Past history of the present disease:—Patient informs that about 4 years ago there appeared an eruption of small elements exactly identical with the present one, accompanied by ostalgiae and arthralgias as well, both symptoms ceasing of themselves. From that time onward, he has been attacked several times by eruptions of the same kind. Description of the lesions and their location:—Eruption constituted by small papules of flattened appearance, but encased in the upper layer of the derm, with follicular or perifollicular seat and disseminated over the limbs and trunk, and as for the latter, mainly over the flanks, on the anterior and inferior part of the trunk. Apart
from these points, a larger quantity of eruptive elements is to be seen on the extensional face of the limbs, chiefly on bony saliences, such as the elbows and knees, forearms and legs, middle and lower parts of the buttocks, juxtrochanteric regions, small articulations of the hands and feet. On the extensional faces, on certain zones of the flanks, of the abdominal wall, etc., the surface of the papules is smooth and depressed, there existing cones of follicular keratosis which lend the whole a molluscoid aspect (i.e. molluscum contagiosum). The small papules are straw yellow, consistent, sessile, and their bases are surrounded by thin erythematous halos. Examinations: — Renal examination show pyelonephritis.

Pathologic histology: — We shall appreciate, in toto, the chief histopathological aspects of both cases. Besides the usual technique of haematoxylin-eosin, we used the argentation of melanin followed by Masson’s trichromic, Mallory’s and Weigert’s stainings, Unna’s polychromic blue-acid orcein, carbol-green of methyl-pyronin, etc. Epidermis: — No noteworthy changes are observed, save a certain degree of thinness of the epithelium in some spots of Case I. The interpapillary prolongations are reduced to a minimum in some points. In Case I, there are also to be seen numerous pigment-laden basal cells, the pigment lying at its habitual juxtanuclear position. Papillary body: — Papillae generally short and broad, in rare points elongated and narrowed. In Case I, under the epidermis, where infiltration is more intense, there is to be seen a narrow band of tissue, in which the corium looks normal. Some widened papillary vessels are seen with swollen endothelial cells, which present foaming cytoplasm with pyknotic nucleus or without any nucleus. Corium: — In the corium we met with the maximum of changes, with the difference that in Case II they consist of a special infiltration in the form of small, generally perivascular or periglandular nodules, while in Case I we are dealing with a diffused infiltration. The differences continue as far as the cellular types are concerned. In both cases, xanthomatous cells are present, constituting the majority or almost the totality of the elements, with classical structure, foamy and granular protoplasm, excentric nucleus, sharp membrane. Yet in Case II, the xanthomatous nodules have a deep location. In the upper derm, around the vessels there exists an infiltration of epithelioid cells and histiocytes. In Case I, there also exist cells of this type, but in small number. In this case, at several points xanthomisation of vascular walls is observed, in general of dermic veins. We already have remarked that in Case I the infiltration is not delimited, extending insensibly in the direction of normal tissue, presenting all transitional forms from fixed connective
cells to large xanthomatous cells. Colagen and elastin are present even in foci of larger xanthomatous infiltration, compressed or reduced to a fine network which, at times, individualizes every cell, but showing no evidence of degeneration.

_Histochemistry:_—The observation of slides, hardened in 10% formol and placed under a polarization microscope, enabled us to verify the presence of amorphous masses and whitish needles (anisotropic substances) not merely within but also without the xanthomatous cells. These formations disappeared on application of heat and reappeared on cooling, showing the typical aspect of the Maltese cross: this has been verified in Case I alone. Both cases were subjected to the staining tests elective for cholesterol, fatty acids, neutral fats and lipoides in general, with the following result: Nile Blue — dark blue or, in certain points, reddish-blue; Sudan III — brownish-red; Scarlet R — brownish-red; Kultschitzki's method — violaceous; Moleschott-Golodetz's reagent — brownish.

_Pathological chemistry:_—Investigations were made on blood serum, urine, and tissues.

1.° _Cholesterol._—For blood serum we used Myers-Wardell’s colorimetric technique; for urine, Gardner and Gainsborough’s extraction technique and colorimetric dosage. With regard to the growths of Case I: weighing of the tumor after previous removal of the epithelial parts, representing the moist weight; dessication at 110° C. until constant weight, trituration and weighing, representing the dry weight by the difference from the moist weight. Extraction from the dry tumor by means of heated chloroform and colorimetric dosage in the liquid of chloroformic extraction. We think the dosage expressed in masts.% of dry tumor represents better the existing contents in the examined part: the values expressed in 100 of moist tumor are liable to variations of water contents, and therefore do not represent evidence so exact as the former.

2.° _Fatty acids._—The technique used was that of Stewart and White, modified by Himwich, Friedmann and Spiers (1931).

3.° _Lecithin._—We adopted Bloor's extraction technique, lipid phosphorus being dosed by Fiske and Subbarow's technique.

4.° _Glucose in total blood._—Dosage of glucose was made by Folin’s technique (1932) on capillary blood from digital puncture (0,1 cc.).

5.° _Total protides._—They were dosed by Abbe-Zeiss’ refractometer on the basis of Reiss-Robertson’s technique with a correction factor for lipids.
# Table 1

**Lipemia**

(Values calculated in mgrs. per 100 cc.)

<table>
<thead>
<tr>
<th></th>
<th>Total fatty acids</th>
<th>Lechithin</th>
<th>Cholesterol</th>
<th>Ratio</th>
<th>Percents from the Total</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Fatty Ac.</td>
<td>Lechithin</td>
</tr>
<tr>
<td>Case I</td>
<td>827</td>
<td>1370</td>
<td>576</td>
<td>1.43</td>
<td>2.20</td>
</tr>
<tr>
<td>Case II</td>
<td>790</td>
<td>935</td>
<td>810</td>
<td>0.97</td>
<td>1.20</td>
</tr>
</tbody>
</table>
The results obtained were as follows:


b) Test of induced hyperglycemia (ingestion of 120 grs. of glucose dissolved in water) (19-9-33): before test — 0.83 gr. of glucose, one hour after test — 1.53 gr., 3 hours after — 1.00 gr. (there was no glycosuria).

c) In urine — Cholesterol: three dosages gave 38.3-43.0 and 40.0 mgr. per liter of urine.

d) In the tumor — Cholesterol (100 grs. dry tissue): 5.12 grs., idem (100 grs. moist): 1.02 gr. Lecithin: (100 grs. dry): 10.1 grs., idem (100 grs. moist): 2.02 grs., P being calculated (100 grs. dry): 0.40 gr.

Other blood analysis (per 1000 cc.)

<table>
<thead>
<tr>
<th>Glucose</th>
<th>Proteins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case I</td>
<td>1.25</td>
</tr>
<tr>
<td>Case II</td>
<td>1.05</td>
</tr>
</tbody>
</table>

Urine

Mgss. of Cholesterol in 1000 cc.

<table>
<thead>
<tr>
<th>Case I</th>
<th>38.3</th>
<th>43.0</th>
<th>40.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case II</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Tumor (Case I)

<table>
<thead>
<tr>
<th>In 100 cc. of</th>
<th>Cholesterol</th>
<th>Lecithin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry Tissue</td>
<td>5.12</td>
<td>10.1</td>
</tr>
<tr>
<td>Wet Tissue</td>
<td>1.02</td>
<td>2.02</td>
</tr>
</tbody>
</table>

Case II. — a) In blood (per 100 cc. of plasma) — Cholesterol: 810 mgr. Lecithin: 935 mgr. Fatt yacids: 790 mgr. Ratio of Fatty acids/Cholesterol: 0.97. Ratio of Lecithin/Cholesterol: 1.15. Ratio of Fatty acids/Lecithin: 0.84. Values per hundred of the total amount in lipides

b) In urine — Cholesterol: absent. Microscopical examination of sediment: hyalin casts in small number and rare red blood cells. Many white cells.

Treatment: Case I.—Insulin injections («Novo» and «Leo»).

4-9-33: 8 units.

11-9-33: 15 units.

13-9-33: 20 units.

Henceforth, 20 units every two days up to the total sum of 280 units. Result: clinically, none; humorally, improvement of the humoral syndrome as may be verified by the charts.

Case II.—Insulin injections («Leo»).

29-9-33: 10 units.

2-10-33: 15 units.

4-10-33: 20 units.

We continued up to the total sum of 105 units. Result: complete disappearance of the lesions, with relative persistence of same on the elbows.

It was observed reduction of cholesterol to 510 and 480 mgrs. per 100 cc. and of glucose to 0,77 gr. per 1000 cc.

Loading test:—Following Buerger’s technique, we administered to one of the patient (Case I), on an empty stomach, 5 grs. of cholesterol in 100 grs. of olive oil. Dosage of cholesterol at the end of 4, 8 and 24 24 hours. The results (positive curve) are to be seen in the chart, side by side with the normal readings.

Functional examination of skin.—For the purpose of investigation of skin responsiveness of these patients, we endeavoured to learn the manner in which they would react to intradermal injection of their own infiltration substances. Still, an investigation with neutral fats and phosphatides (lecithins) may be unsafe in case of a latent infection (lues, etc.). We, therefore, availed ourselves of the cholesterol itself, in the following manner:
Charts 2 and 3
Case I. — a) Intradermal injection on the volar face of the right forearm of 0.1 cc. of purified olive oil containing 0.5% of cholesterol: positive reaction, papule with erythematous halo, fairly visible up to 5 days. After this time, regression with pigmentary reliquat. Absence of isomorphism on the spot of the intradermal injection as well as on the points of medicamental hypodermic injection (insulin); b) intradermal injection of 0.1 cc of purified olive oil into the left forearm: doubtful reaction, red circle and diffused tumefaction lasting 48 hours.

Case II. — a) Intradermal injection of cholesterol in olive oil: doubtful reaction, red circle and diffused tumefaction lasting 48 hours; b) intradermal injection of pure olive oil: negative reaction.

The clear contrast afforded by these two patients may, therefore, be summarized as follows: 1) differences in the locations and extension of the disease; 2) differences in the objective morphology of the lesions; 3) differences in the clinical evolution, as in Case I the course was chronic and the lesions isolated, and in Case II the course was acute in the form of attacks, the lesions abundant and disseminated; 4) existence of reactions of hypersensitiveness — in Case I: pigmentary reaction and allergic reaction to cholesterol; in Case II: sub-icterus, and peri-follicular lesions surrounded by an erythematous halo; finally, 5) in both patients with the same metabolic disturbance of lipides occurring, there was observed: in Case I a primary cholesteroluria without renal lesion, while in Case II, in the presence of a slight albuminuria with hyalin casts, there was no elimination of cholesterol through the urine. This evidence, on the whole, indicated the way in which to proceed for the explanation of same: this interpretation may perhaps rest on the considerations which follow, being intended furthermore for the choice of a criterion concerning the study of lipidoses in general.

II. ESSENTIAL CHOLESTEROLURIA IN XANTHELASMA

Normally, urine excretes only very small quantities of cholesterol. Almost the whole cholesterol is conveyed outwards through gall and intestine. Bacmeister and Pribram observed only traces of this compound in normal urine. Gardner and Gainsborough obtained for normal urine an excretion of about 4 mgrs. of cholesterol per diem, Gerard 0.23 mgr. in 24 hours as a normal quantity. In pathological case, Kaiserling-Orgler and Munk observed the presence of birefringent corpuscles in urine of nephrotic patients, which corpuscles seem to correspond to cholesterol esters, nearly always present when the kidney
Curva normal (segundo Bürger)
Normal curve after ingestion of 5% of cholesterol (Bürger)

Charts 4 and 5
presents cellular degenerations. It is mainly in nephrosis of the lipoidic type that cholesterol is excreted in appreciable quantities. Condorelli, in numerous analyses of normal urine, verified that cholesterol is a constant element, being excreted in the form of oleic ester, in the proportion of 15 mgs per diem. According to Gardner and Gainsborough, in urine there is a great deal of cholesterol eliminated in the form of cholesterolic sulphate. Apart from the cholesterol hydrolysable by acids and alkalies, in urine there seems also to exist a free cholesterol of lesser pathological importance.

The case we now present is that of a patient with disseminated xanthelasma without renal lesion, who shows accentuated cholesteroluria. The dosage of serum cholesterol revealed the high rate of 576 mgs per 100 cc., and the average elimination through urine oscillated around 40 mgs per liter. Appreciating, side by side, this case and the other analogous one, also with hypercholesterolemia (810 mgs per 100 cc.) but without elimination of cholesterol through urine though presenting renal lesions, we are led to give credence that the first case clearly represents a primary cholesteroluria in connexion with a xanthelasmic disease (Case I).

The fact pointed out is rather rare, and above all hard to account for, when there exist no lesions of renal tubules. By the way, even in this case in which the presence of cholesterol implies a lipoidic degenerative process, the direct passage of that element from plasma to urine is generally not admitted, provided the kidney does not allow it to pass. If the fact occurs with biliary acids (by the way, chemically analogous to esterol), it is due (Thannhauser) to the COOH group of the side-chain, a fact which is also verified with regard to porphyrins, as uroporphyrin is a polycarboxylate derivative. On the other hand, in this case the habitual excretory ways of cholesterol intervene, i.e. its passage through gall, blood and also skin, approximately at the rate of 0.10 gr. At any rate, as is well known, under pathological circumstances cholesterol may accumulate not merely in blood, but also in certain endocrine organs and others, a lipoidic degeneration of their cells not being necessary.

Now it is convenient to recall the analogy of certain etiologic factors common to xanthelasma and lipidic renal degenerations: infections (lues, etc.), endocrinic disturbances of pregnancy, of hyperthyroidism (Epstein), etc. The same occurs with the blood state, with the decrease of osmotico-colloidal pressure, already demonstrated in lipidic nephrosis by Krogh and Schade, seems to depend upon the great decrease of albumin contents, while the probable colloidal disturbance,
admitted by Bloch and Schaaf in xanthelasma, would be the proper expression of the absolute and relative modifications of the contents in lipides. The question of interrelationship between cholesteroluria and the state of infiltration or lipidic degeneration in cases of xanthelasma and nephrosis respectively, is still awaiting solution.

In case of nephrosis, some authors like Schmidt admitted lipidemia to be a primary process until the time the epithelial degeneration allows the passage of cholesterol, or rather its elimination in the inner part of the desquamative cells, according to Tietz. Generally speaking, the views have been turned, as in case of xanthelasma, towards functional anomalies of the liver in order to account for the metabolic disorders not merely of cholesterol but also of protides. In both affections, the respective changes of lipides and protides might not constitute the sole pathological process, and in certain cases not even the most important. Some authors like Epstein go so far as to recommend the substitution of «lipoidic nephrosis» by «albuminuric diabetes».

As far as xanthelasma is concerned, we have very little through knowledge, and it seems to be certain that the classical conception of the deposit of cholesterol in the tissues as a «cholesterinic tophus» (Chauffard and Laroche) does not answer a number of important questions. The idea of cholesterol deposited as a foreign body in the tissues, perhaps suggested by Touton's histological findings (giant cells due to a foreign body) and by Lebedew and Anitchkow's classical experiments, is not admitted at present. In most cases, if not in their totality, we are dealing with a reversible process rather suited to the hypothesis of a progressive infiltration in which the tissues would play an active rôle in accordance with their qualities.

However, the coincidence existing between certain etiopathogenic factors of nephrosis and xanthelasma is perhaps able to aid the study of both affections. A good proof of this is afforded by the occurrence of the hepatic disturbances already mentioned, frequently observed in either of them but better known in nephrosis. It is known, for instance, that fibrinogen increases in the latter affection, surpassing the average 0.42 gr. and reaching 0.60 and even 0.90 gr. In nephrotic children, Knauer nearly always verified hypoglycemia, etc. Still, the most important fact, without any doubt, lies in the alteration of the ratio A/G, which in normal plasma is equal to 1.3-2.8: this ratio decreases, and is often inverted. The loss of albumin through urine, at length, affects the composition of plasma so that its contents in serins greatly decrease. The albuminuria might be compensated by a larger production of serins and globulins so as to maintain the osmotic equilibrium of plasma and
prevent edema. However, in accordance with the experiments of Kerr, Hurwitz and Whipple on dogs subjected to plasmapheresis, it occurs that the liver, very compliant in desponding with increase of globulins, is on the contrary slow in producing albumins. In this lies the cause of decrease and inversion of ratio G/G.

Now, an identical fact has already been observed by Abrami in xanthelasma, i.e. an obvious decrease of ratio A/G, the value of the albumin fraction being 2.0 gr. %. Yet, there was something extraordinary: absence of renal symptoms, no albuminuria, no edema. There was, to be sure, a high lipidemia: 320 mgs. % for neutral fats, 800 mgs. % for cholesterol, apart from cholesteroluria and presence of birefringent crystals in urine. However, as already said, it was a case of disseminated xanthelasma, these alterations of lipides being thus justified.

This is one of the cases we referred to as being able to aid the better knowledge of both affections. As far as nephrosis is concerned, it is doubtful, on the one hand, whether there exists any constant relationship between albuminuria and lipoidic infiltration of kidney; on the other hand, whether hypoproteinemia is always in connexion with nephrotic edema. In case of xanthelasma, as it occurred with the patient of Abrami and with that of our observation, it is a very old fact that so intense a lipidemia and moreover, cholesteroluria could exist without the least trace of a renal lesion: we shall see how to interpret the phenomenon in the best manner.

Although cholesterol completes the picture of nephrosis, it does not seem to show an evident relationship of cause and effect: this is the opinion of the most modern authors like Bennett, Murphy, Maxwell, Calwin-Goldberg. The hypercholesteroluria of nephrosis seems to be endogenous, because food does not influence it: in accordance with Gardner, Shapiro, this modality of the compound would be the only one which passes through the kidney. In xanthelasma it is, likewise, thought at present that alimentary cholesterol is of a very relative value; on this point there is no more accordance with the idea defended by Chauffard and Laroche. As far as cholesterol is concerned, some authors like Murphy would have observed birefringent lipoides in urine prior to supervention of hypercholesterolemia; others like Grunke found no relation between the excreted lipide and its concentration in blood, One of us chanced to find hypercholesteroluria every time that plasma cholesterol was more than 320 mgs. % (nephrosis). Nevertheless, in the present case we observed that insulin injections, though lowering the contents of blood cholesterol more than 50 %, exerted no influence on the elimination of urine cholesterol.
In our opinion, apart from this relationship between lipidaemia and lipiduria, it is fairly possible that Buerger is right in thinking that the cholesterol of nephrotics comes from cells destroyed in the organism. Thus there might be produced a cytolytic cholesterol, different from that encountered in pregnancy, diabetes, choleemia or xanthelasma. Amongst others, Stepp and Elwyn laid stress on the importance of the lesion of the parenchyma and glomerulus, as being primary factors of the nephrotic syndrome; the same idea is, in an analogous way, supported by Widal's School. In such conditions, cholesteroluria ought to be considered as a part of the general impregnation by esters of cholesterol, indicating perhaps a real diathetic state. Such is the opinion of Hempel and Sokolow, and Tuskow, who have observed the phenomenon as we did. All cases of Lawrinowitch who produced a work on the question of the elimination of anisotropic fats through urine, refer to several renal affections, acute and chronic as well, including a case of amyloidosis, in which cholesteroluria was abundant. None of the patients presented skin xanthelasma, while in all of them there were more or less severe lesions of the parenchyma and renal epithelium. That author considers «myelinosis» (Anitchkow) of kidneys as a result of «the general tendency of the organism towards cholesterinic impregnation». In the other cases of literature (Sokolow and others) there was coexistence of skin xanthelasma and renal lithiasis. With the exception of Hempel and Sokolow who found 55 mgrs. % of cholesterol in urine, the others do not report the eliminated quantity.

The other aspect of the question is that of the relationship between the state of blood and the production of edema. As we have seen, the latter is absent in cases of disseminated xanthelasma, even when the contents in albumins were low and those of cholesterol high.

The study of the relationship between edema and hypercholesterolemia has lately been ventilated chiefly by Heilig and Lederer, Calwin and Goldberg, Bring and Heckscher, Maxwell. For some authors, the degree of oedema is proportional to the quantity of cholesterol in plasma (Heilig and Lederer). There exists no renal edema, says Bennett, unless this lipide is found to be increased.

Nevertheless, in studying the curves of cholesterolemia and volume of edema, Maxwell was not able to observe any parallelism between them, although he always found increased contents of lipide. Cowie, Jarvis and Cooperstork also studied a case of nephrosis, in which cholesterol was rather high (525 mgrs. %), without presence of edema. Calwin and Goldberg, from the examination of several patients of nephrosis and glomerulo-nephritis, infer that there is no relationship of
cause and effect between cholesterolemia and edema. In the case studied by them, edema decreased until its complete disappearance, the contents in cholesterol not undergoing, after all, any sensible depression. Generally speaking, one may conclude that the values of cholesterol in plasma vary directly in cases of renal patients, yet without proportionality to the degree of edema, though they increase in periods of larger edema and irregularly decrease along with the decrease of the edema.

Let us now consider the relationship existing between edema and hypoproteinemia. Weech and Long consider as a critical point for proteins that of 5.0 grs. %, and 2.5 grs. % for the albumin fraction: below these values oedema would assert itself in cases of its resulting from undernutrition. For the case of nephritic oedema, Fahr, Kerkhoff and Conklin verified the percentage of 4.8 grs. %. The figures obtained by one of us were always lower than 5.1 grs. %. Analogous results were obtained by Peters and collaborators, with the difference that these authors were able to verify oedema without hypoproteinemia in the first stages of the disease.

As we believe, it may be stated that the cause of the oedema of nephrotics seems, most likely, to be intimately connected with the contents of plasma in protides. Nevertheless, a number of facts observed invite great circumspection in such a statement. On one hand, the history of hepatic cirrhoses, of hepatosplenic amyloidoses without nephrititis, of certain infestative conditions etc. demonstrates that the hypoproteinemic syndrome may be frequently observed without any renal lesion; on the other hand, the history of certain cases of disseminated xanthelasma teaches that a syndrome of hyperlipidemia and lipiduria, accompanied or not by hyperprolithemia, may occur without edema or albuminuria and may, consequently, be exempt from any renal factor.

The various aspects of this important question being thus appreciated, we cannot but repeat once more what we wrote about the importance which, in our opinion, lies in hepatic disturbances, at least as a concurrent cause in the pathogenesis of nephrosis and xanthelasma. On this point we disagree with Abrami when he endeavors to insist upon the primordial rôle of renal alterations. The role of the thyroid gland seems to be evident in certain cases, though we admit it with restrictions, as Lichtwitz does. As for us, we continue to prefer an eclectic criterion, admitting that several causes may lead to the same end. Should the disparity of thyroid equilibrium always be in a sense of decrease, as Epstein stated? It is not certain, for in certain cases opotherapy greatly impairs the patients with nephrosis and, on the other
hand, an exact evaluation of basal metabolism is impossible in individuals affected by anasarca. Besides, the improvement obtained, for instance, by Christic, Hollender and one of us through administration of thyroid to patients of xanthelasma, perhaps may not suffice to justify one's speaking of the constant causal role of thyroid insufficiency.

How should we then account for the primum movens of the metabolic disturbance of lipides, the basis of pathogenesis of nephrosis and xanthelasma? This is unknown as yet: nevertheless, as far as the case of xanthelasma is concerned, certain facts occur which, in our opinion, to a certain extent can make its etio-pathogenesis a little more clear.

III. ROLE OF PREDISPOSITION IN XANTHELASMA

In spite of the knowledge of some facts very well observed, attention was not yet drawn sufficiently to the incidence of phenomena of local action in the pathogenesis of xanthelasma. Now, the importance of certain local conditions is at once evident, on the first examination. In our opinion, several phenomena tell in their favour; amongst which are the locations, the objective morphology, and the clinical evolution of xanthelasma.

Endeavouring to synthetize the group of facts which seem to bring into evidence the action of predispositional factors in xanthelasma, we have:

1) Locations: — a) on the eyelids, extremities and extensional faces of the limbs, juxarticular regions subject to attrition; b) nervous tracts and territories of segmental projection; c) pilosebaceous follicles.

2) Objective morphology: — a) flat lesions or growths in the form of tumors, isolated; b) lesions in the form of corymbs, band, or garland; c) disseminated lesions, surrounded by an erythematous halo; d) lesions undergoing evolutive or eruptive metamorphism (for instance, erythematous patches, papules and vesicles in the syndrome of Kerl and Urbach).

3) Clinical evolution: — a) chronic course with isolated lesions; b) acute course with lesions extraordinarily abundant; c) coexistence of other skin syndromes such as follicular keratosis, comedonan acne, psoriasis, lichen planus, neurodermitis, prurigo, zoster, vitiligo, keloids; d) coexistence of extracutaneous syndromes such as gout, asthma, hepatic cirrhosis, syndrome of Schuller-Christian, renal lithiasis, atheroma, diabetes, etc.; e) occurrence of certain humoral syndromes such as hyperlipidemia, hypoprotidemia, hyperglycemia, etc.

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1 This denomination follows the classification of Urbach.
4) Reactions of hypersensitiveness: — a) pigmented reaction; b) isomorphic reaction; c) allergic reaction.

5) Heredity: — the question of the so-called « xanthoma juvenilis ».

For the case of xanthelasma diabeticorum, Jaddassohn as early as 1904 formulated a pathogenic theory with which the one we defend today is in fair harmony: in his theory the concurrent factor is the action of a toxico-necrobiogenic or phlogogenic agent in traumatized regions, or in determined sites such as the pilosebaceous follicles. An analogous interpretation was given to xanthelasma palpebrarum, accompanied by definite or latent disturbances: « Eine Praedisposition zur Xanthombildung muss naturlich bei diesen beiden Formen vorhanden sein, und zwar eine an den verschiedenen Körperteilen verschiedenste Praedisposition » (A predisposition to the formation of xanthoma must, of course, exist in both these forms, that is to say a differing predisposition on different spots of the body). The existence of this predisposition is indicated by the main locations of xanthelasma: eyelids, juxta- and para-articular regions, territories of segmental projection, pilosebaceous follicles. Out of these locations two — articular regions and pilosebaceous follicles — are usually to be observed in affections which are accompanied by hyperergy. By the way, this hyperergy is also suggested by the clinical evolution and by the morphology of the lesions. From the evolutive viewpoint, we have two principal clinical modalities: the chronic course with isolated tumor-shaped lesions, the acute course with extraordinarily abundant lesions.

What are the reasons of these differences, if not fortuitous causes connected with the predisposition of the patient? In the first case, a circumscription of pathological productions occurs dependent, to be sure, upon the same causes as those which disseminate the lesions in the second case. The beginning of the lesions is, by the way, often observed on the eyelids, followed later on by a generalized eruption as if the factors of circumscription ceased to act in the presence of the causes of dissemination. The phenomenon runs in the same manner in certain diseases of sensitiveness, v. g. eczema, artificial dermalites, etc., as a consequence of the gradual formation of refractory zones at the cost of receptive ones. This is what is learned, with the greatest possible clarity, from the examination of the objective morphology of xanthelasma. Either isolated tumor-shaped lesions are constituted, or on the contrary micropapulous lesions grouped in the form of band, corymb, etc., are disseminated.

The central healing of the lesions, with formation of peripheral rings, is habitually considered characteristic of parasital dermatooses. But
what occurs in this particular with regard to trichophytoses has also been verified in other affections of insufficiently elucidated etiology or pathogenesis. The difference between the behaviour of skin in the immediate neighbourhood of the lesions already healed and the lesions still growing is of fundamental importance. Kropaschek and Linser, Woronoff observed annular formations on irradiated skin and in psoriasis: the peripheral ring seems to indicate the cessation of the growing of the lesion and the spontaneous cure. It is not impossible that the factor of dissemination gradually disappears up to the inner border of the ring, or penetrates the ring but without pathogenic capacity. The case is simplified when it passes from xanthelasma to a well known disease such as lues or trichophytosis: in such case, the factor of dissemination intermingles with the causal germ; as far as the factor of circumcision is concerned, it does not vary, for in any case it is represented by the immunizing process of the organism. Often a central relapse is observed (syndrome of Kerl and Urbach), and if the phenomenon repeats itself in spots more and more excentrical, lesions are constituted in the form of cockade. It may also occur that two neighbouring rings meet in their centrifugal march: they grow but in the direction of the zones respectively immune, and the result is the spontaneous cure at the zone of contact.

A fine instance of these morphological variations is afforded by the type «xanthelasma areolar multiplex» of Arzt, and by the syndrome of «extracellular cholesterinosis» of Kerl and Urbach. In the latter, the lesions even assume a great metamorphism, become tumescent and red-cyanotic, recalling erythema exsudativum multiforme. In xanthelasma areolar multiplex there also occur serpiginous lesions which deserve an interpretation analogous to the preceding, only that in case of serpiginous lesion there is a mutation of polarity: immunization zones are not constituted, any more, around a central point, but in the direction of lines of minor resistance which remained exempt from the immunization of the tegument. The quick involution at the level of the points which last had been affected is characteristic so that the lesion takes up a serpentine form which gives it its name.

The predilection for the follicular location may be accounted for by the peculiar distribution of the blood vessels of the follicles, as occurs in several haematogenic exanthemae.

To conclude, we will observe that the locations, the morphology, the clinical evolution of xanthelasma approach this syndrome to other symptomatic complexes proper to hyperergizing diseases. However, identical phenomena are also observed in another class of dermatoses, still
closer related to xanthelasma: the toxicodermiae. They, indeed, benefit by all the explanations given hitherto, and applied to infectious hyper-ergetic manifestations; it therefore seems needless to insist upon the matter, because it would oblige us to repeat facts already known.

The criterion for the study suitable to be adopted with regard to skin lipidoses ought to coincide with the same directive lines which caused the question of toxicodermias to progress, i. e. the verification of the occurrence of phenomena of hypersensitiveness to toxics, medicaments or metabolic products.

SUMMARY AND CONCLUSIONS

1. In the present paper two cases of xanthelasmatisis (xanthoma) with marked changes in lipid and sterol metabolism are studied.
2. One of the cases without renal injuries shows accentuated cholester-oluria, while the other with renal injuries presented pyelonephritis without cholesteroluria.
3. Cholesterol, total fatty acids and lecithine give high values in both cases. Histo-chemical and polariscopic researches confirmed a real infiltration of cholesterol and lipids in tissues.
4. Burger’s test in case I may be seen as a lack of tolerance to cholesterol.
5. Although insulin treatment decreased the cholesterol and glucose content of the blood in case I, it was not effective in relieving the clinical picture. In case II a reduction of cholesterol and glucose of the blood and a rapid disappearance of the growths was obtained.
6. Intradermal reaction with cholesterol in case I was positive, showing, therefore, a hypensensibilization, of the skin to infiltration substances.
7. Clinico-morphological aspects of the cases studies indicated a clear cutaneous sensitisation.
8. Xanthelasmatisis (xanthoma) has been compared with toxic cutaneous diseases with the conclusion that the same methods must be adapted for the study of skin lipidosis as for toxidermic diseases.

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