LIPOIDOSES AND SCLEROMALACIA PERFORANS

BY

J. VAN DER HOEVE

WITH 28 ILLUSTRATIONS ON FOLDING PICTURES

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In 1931 [1]) I designated as scleromalacia perforans, a disease, one of the principal symptoms of which is the appearance of gaps in the sclera, which usually affect the entire thickness of this membrane of the eye, so that a perforation of the sclerotic coat arises resulting in holes of the sclera.

On clinical and morbid anatomical examination, inflammation is found to play but an inferior part in this affection of the sclera, the process is more suggestive of a degeneration and softening of the tissue, Mylius [2]) even speaks of a "complete liquefaction", so that the term "scleromalacia perforans" may be regarded as being very effective.

G. F. ROCHAT [3]) who contemplated designating this affection "scleritis necroticans" was willing to have this name replaced by "scleromalacia perforans", which term was soon used in all ophthalmological circles. In many places new cases were observed, in our country twelve, so that the affection is not so rare as it was at first thought to be.

The external aspect of the eye in this affection depends on the number, size and site of the defects and on the condition of the conjunctiva bulbi covering these defects. The conjunctiva may not be changed at all or it may be entirely absent at the site and it may be in any condition conceivable between these two extremes. Often it is observed that a defect in the sclera is only more or less covered by mere frays of the conjunctiva. The affection of the sclera is bilateral in almost all cases.

The number of defects may vary (fig. XVI, XVII, XVIII, XIX, fig. XV), the size ranging from small fissures (fig. XVI) or points to vast gaps, covering the greater part of the sclera of an eye (fig. XXIV). Large holes may result from a small one having increased in size, the edges often appear ragged. They may arise by the confluence of several holes, which is often clearly visible when looking at the form (fig. XV). The holes that become confluent afterwards are often separated by very thin remains of the sclera (fig. XXI).

The site of the defects may vary from far behind the equator (fig. XXI) to the front, near the cornea in the socalled intercalary part of the sclera, which is one of the boundaries of the anterior chamber (fig. XVI, XVII, XVIII, XIX).

When the perforation is situated in the intercalary part, the aqueous humor may escape or the iris may protrude. If the conjunctiva is absent over the defect the aqueous humor may continue to stream so that the eye remains soft and the anterior chamber of the eye is very shallow; also an entirely bare prolapse of the iris may arise.

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[1]) Meeting Dutch Society for Ophthalmology, 17. May 1931. Ned. Tijdschr. v. Geneesk. 1931, 12 Sept., page 4733.

[2]) K. MYLIUS, Rheumatismus und Auge, 1942, page 76. Der Rheumatismus, Vol. 22.

[3]) Ned. Tijdschr. v. Geneesk. 1933, page 1935.

When the conjunctiva is present the aqueous humor may accumulate below it so that a kind of cyst is formed (fig. XVI) which closely resembles a cystous scar as may be found following extraction of a cataract, and such as we endeavour to obtain in LAGRANGE's or ELLIOT's operations in cases of glaucoma.

We may also find a prolapse of the iris partly or totally covered by the conjunctiva (fig. XVII and XVIII).

If the openings of the perforation are situated in a posterior region, the ciliary body or the chorioid may be lying in the hole, partly or entirely covered by the conjunctiva or otherwise quite bare. In this connection it is striking to see that the uvea usually does not protrude in these holes, we get the impression that the chorioid, tightened by the tensor chorioideae is perfectly capable of bearing the normal ocular tension.

When studying the clinical picture of the blue sclerotics in which the sclera may be much thinner than it is normally, it struck the observers that no protrusion and formation of staphyloma takes place; here it became evident that the uvea, in conjunction with a thin layer of sclera, is capable of resisting the ocular tension. Our observations in scleromalacia perforans show that the uvea is even able to do so all by itself. This could be expected, for we know that sclera and chorioid are separated by the perichorioidal lymph space, which in our opinion has the function of transporting the ocular humours to the posterior lymph vessels, for this to occur it is necessary that the chorioid bears the ocular tension and is not pressed against the sclera by this tension.

An entirely different situation arises when the ocular tension is increased, then the chorioid is pressed against the sclera or protrudes through an opening in the sclera.

Later we will describe the clinical picture of scleromalacia perforans as accurately as possible using case histories of patients observed by ourselves or recorded in literature.

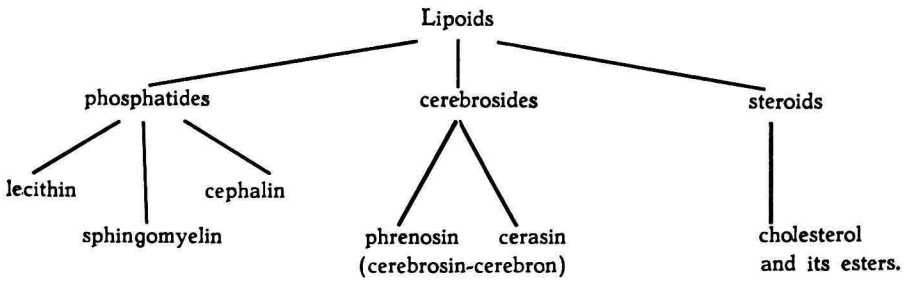
Lipoidoses are syndromes, one of the principal symptoms of which is a disturbance of the metabolism of one or more lipoids.

Lipoids are extremely important substances for the human organism, veritable materials of the cell, they constitute an essential part of the cells, which are entirely impregnated with them.

Until a short time ago the lipoids were divided into five classes phosphatides, sulfatides, cerebrosides, protagon, steroids.

Only a few representatives of the sulfatides were found in the human body, the phosphatide-sulfuric acid cerebroside (KOCH) and the phosphorus-free sulfatide (LEVENE), both found in the brain substance; they could be inserted into other classes. Protagon was found not to be a chemically pure substance but a compound of cerebrosides and phosphatides, just as cuorin, which was at first regarded as a phosphatide and jecorin, which was thought to be a compound of lecithin and glucose, were

afterwards found not to be pure chemical substances but in all probability compounds. Since then these two classes are no longer used and the classification is as follows:



Their very names reveal that many lipoids are closely connected with the central nervous system.

The lipoidoses that are recognized at present, are syndromes that were already known prior to the conception of lipoid being advanced in biochemistry comparatively recently, whilst not until some time afterwards its relationship with the lipoids was observed, and it is very likely that in the course of time more diseases will be grouped under the heading "lipoidoses".

At present are recognized as such: TAY–SACHS disease, GAUCHER's disease and NIEMANN–PICK's disease.

We are not justified in saying that these diseases are caused by a disturbance of lipoid metabolism, it is possible that both lipoid disturbance and disease are symptoms of a more extensive syndrome, without the former being necessarily dependent on the latter.

GAUCHER's disease was described by himself in 1882. He was of opinion that the enlargement of the spleen observed by him in a child was due to a primary carcinoma of this organ; not until the year 1907 was the affection recognized as an affection of a system, the metabolic character of which was recognized in 1916, and its lipoid nature in 1924. The principal symptoms are enlargement of spleen and liver (therefore this disease is also termed spleno-hepato-megaly) as part of an affection of the entire hematopoietic system, also of the bone marrow and the internal lymph glands. A characteristic symptom of this disease is the presence of the GAUCHER's cells, swollen, clear, translucent, round, epitheloid cells with round nuclei. The disease mostly affects the female sex, is familial, it begins in youth and runs a chronic course. The lipoid character is demonstrated by an enormous increase of one of the cerebrosides, cerasin, which is to be found in the GAUCHER's cells in such amounts as to constitute up to ten per cent of the dry substance of the spleen. We may therefore term GAUCHER's disease "Hyperlipoidosis cerebrosidica cerasinica".

A second important lipoidosis was described by NIEMANN in 1914, this affection is known as NIEMANN–PICK's disease. It occurs especially in girls. Besides the enormous enlargements of liver and spleen, affections of the bone marrow and glands, which occur also in GAUCHER's disease,

the thymus and the adrenal gland are affected in NIEMANN–PICK's disease.

This disease runs a much faster and more malign course than GAUCHER's disease whilst in the latter the patients sometimes grow as old as fifty years, the young patients affected with NIEMANN–PICK's lipoidosis usually die when still very young.

Here a phosphatide is concerned, lecithin, which is present in far too high a quantity, sometimes even eighty times as much as in normal subjects (6.4 per cent whereas normally 0.08 per cent), so that we are justified in designating this disease as hyperlipoidosis phosphatidica lecithinica.

Besides an increase of lecithin an increase of the cholesterol content is found as well, sometimes five times as much, as normal, which is not surprising for as we will see later it is probably the liver that regulates cholesterol metabolism, therefore it is all the more remarkable that, in view of the liver being affected to so great an extent, a disturbance of the cholesterol metabolism in GAUCHER's disease is mostly not especially mentioned, as that it is found in NIEMANN–PICK's disease.

A special disease, which afterwards was found to belong to the lipoidosis group, described by TAY in 1881, and by SACHS in 1887; is known as TAY–SACHS disease. Apart from the organs mentioned in connection with the other lipoidoses the central nervous system is affected here as well, both brain and retina.

The young patients are idiots and they are blind as a consequence of this affection, which is the reason why it is also termed amaurotic family idiocy. The ganglion cells especially are affected in this disease. A general hyperlipoidosis exists, accumulation of lecithin is not only found in ganglion cells and in mesenchymal cells in the wall of the vessels of meninges and choroid plexus, but also accumulation of sphingomyelin in liver and spleen, whilst a sugar containing lipoid, composition of which is still unknown, is also found.

Amaurotic idiocy occurs almost exclusively in Jewish children. The two other lipoidoses mentioned above also show a preference for this race.

The third class of lipoids, the steroids, is likewise represented among the lipoidoses by HAND–SCHÜLLER–CHRISTIAN's syndrome, a disturbance of cholesterol metabolism.

It is extremely difficult to define the conception "lipoid" correctly; the best is to adhere to the definition that the literal translation of the word implies and therefore we say: lipoids are substances resembling fat.

It is obvious that so vague a definition may cause the conception "lipoid" to become a collection of a number of substances that may show few if any common features, provided that each of them resembles fat in some way or other. As regards this resemblance any property shown by the fats may be considered: physical, chemical, physico-chemical and others.

Frequently the solubility of these substances is taken as point de départ

and various authors, such as BANG–OVERTON and others present as their definition, with slighter or greater differences: lipoids are substances that, like fats, are insoluble in water or only with difficulty; they dissolve however in organic dissolvents such as ether, alcohol, oils, chloroform, benzol etc. When starting from the chemical composition of the substances one meets with difficulties. From a chemical point of view the body fats, being esterlike compounds of the triatomic alcohol-glycerin with the three higher fatty acids: palmitic acid $C_{16}H_{32}O_2$, stearic acid $C_{18}H_{36}O_2$ and unsaturated oleic acid $C_{18}H_{34}O_2$, rank first with the fats under discussion.

In this respect the phosphatides are very much like these fats and therefore they may be grouped with the lipoids from the chemical point of view, for the phosphatides are likewise esters of glycerin and the three higher fatty acids mentioned above, the only difference being that one of the three OH-groups of glycerin has been replaced by phosphoric acid.

The esters of cholesterol may also be grouped with the fat resembling substances from a chemical point of view, because they, too, are esters of the three fatty acids referred to above, the only difference being that not the triatomic alcohol glycerin but the monoatomic alcohol cholesterol is concerned here.

A chemist, however, will not appreciate the idea of cholesterol being grouped with the lipoids, for cholesterol is an alcohol, and as such it belongs to a different class from the lipoids, therefore cholesterol cannot be a lipoid from a chemical point of view. So we are not surprised at all when reading in HAMMERSTEN's textbook [4]):

"The group of the lipoids cannot be characterized sufficiently from chemical point of view, because substances such as phosphatide, steroids and cerebroside are grouped under this heading, which are chemically so different. From chemical point of view the name of lipoid is not justified."

Yet we shall regard cholesterol here as a lipoid and adhere to the above classification of the lipoids, because cholesterol ressembles body fats in sufficient degree as far as solubility and staining are concerned. Fat stains black with osmic acid and red with Sudan III, whereas cholesterol stains gray and orange respectively with these substances.

It is difficult to define lipoids correctly and when trying to define steroids one also meets with difficulties.

Above we saw how important phosphatides and cerebrosides are for the organism, and the same applies to the steroids.

Ever since science has come to recognize the fact that the steroids are closely related to substances that are as important to life as hormones and vitamines, the significance of these substances has grown to a considerable extent.

According to their origin the steroids are divided into zoosteroids, phytosteroids and mycosteroids. Zoosteroids may be absorbed in the human intestine, their principal representative is cholesterol.

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[4]) C. HAMMERSTEN, Lehrbuch der physiologische Chemie, 9th. ed. 1922, page. 186.

Phytosteroids are not of direct interest to the biology of man, because they pass through the intestine without being absorbed.

The same applies to the mycosteroids, and yet they are of great importance to us, because some of them, e.g. their principal representative "ergosterol", as well as some zoosteroids may be converted into vitamins.

Many hormones, e.g. all sex hormones such as testosteron, oestron, progesteron etc., are among the steroids, one has even succeeded in preparing some of them synthetically, e.g. the important testosteron, taking cholesterol as the point the départ.

The great influence sex hormones may have on the development of the individual is well-known. This influence is shown in experiments on animals and thus we may observe how the sex characteristics may be more or less marked by changing the amount of sex hormone or the sex characteristics may even change into those of the other sex.

External and internal sex organs may be enlarged to an enormous extent owing to the influence of testosteron. In a castrated cock [5]) the comb becomes atrophic following the operation, and may again return to normal size through application of testosteron and its superficies may increase from e.g. 400 to 2700 square mm. In man, too, the sex hormones may change in quantity and quality in certain diseases and correspondingly, the sexual characteristics may be changed; in Cushing's disease a woman may acquire a male appearance which may again be changed occasionally, by operative intervention.

In view of the sex hormones being steroids we are fully justified in grouping similar diseases with the lipoidoses and in view of the possibility of there being too great or too small an amount of sex hormone, or a disturbance of the interplay of the hormones, we may speak of hyper-, hypo- and dyslipoidosis sterinica.

The relation of steroids and vitamins is more complicated than that of hormones and steroids, for vitamins are not steroids, though some steroids may be changed into vitamins by means of a certain treatment, such as irradiation with ultraviolet rays; these steroids are precursors of vitamins, the so-called provitamins.

The vitamins that may arise from myco- or zoosteroids in this way are nearly all D. vitamins, which are very useful when combating rachitis.

Of these provitamins D ergosterol is best-known, which is changed into vitamin D_2 by means of irradiation, the latter is also called calciferol.

When irradiating 7-dehydro-cholesterol vitamin D_3 is produced, whilst irradiation of 22-dehydro-ergosterol provides us with vitamin D_4 which has a powerful antirachitic action. By means of a similar irradiation of myco- and zoosterols proprietary brands are made, such as Vigantol and the well-known Dohyfral tablets, produced by Philips and van Houten, which are used to combat rachitis.

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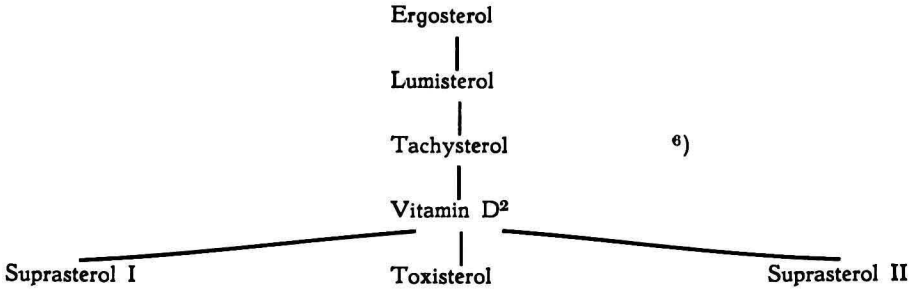
[5]) E. ABDERHALDEN, Lehrbuch der physiologischen Chemie, 7th. ed., 1940, p. 50.

Although irradiation may be a great advantage in this way, grave disadvantages may arise from irradiation, for vitamin D_2 is not the final product of irradiated ergosterol, when further chemical transformations occur highly toxic agents may make their appearance as is shown in the following:



When there is an excess of ergosterol in the stomach or intestine of man, irradiation by the sun or by another source of ultraviolet rays, ergosterol may be converted into toxisterol in the body, which may give rise to highly undesirable symptoms of intoxication. Here we see a striking example of the occurrence of an intoxication by chemical substances under the influence of irradiation of the body.

Another example of a similar intoxication due to chemical transformations following irradiation we find when remembering the eosin-pigs of the first world war. Pigs that were given food denatured by means of eosin, became severely ill when they were exposed to the open air and to sun light, the consequences of this intoxication sometimes being fatal.

A third example is the fact that Roentgenirradiation in pregnant animals may cause the offspring to be born with cataractous lenses, although the animal's abdomen had been protected during irradiation.

It is thought that in this instance a chemical substance similar to choline is formed by the irradiation. Some authors maintain that if pregnant animals are injected with blood of irradiated animals of the same species the offspring may be born with cataractuous lenses.

Patients affected with congenital porphyrinuria may develope skin eruptions and other serious manifestations in the parts of their body exposed, in summer, presumabely due to the action of light. This affection is termed hydroa vacciniforme; it recurs every summer as eczema, necrotic patches and ulcers.

This disease may give rise to severe mutilations; defects of ear and eye, blindness when the cornea is involved, the hands may be disfigured, the fingers stiff and the terminal phalanges may become atrophic, whilst pigmentation and piliation may appear in the skin as a protection, as it were, against the rays.

Furthermore bones and teeth, of both deciduous and permanent dentition

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6) LEHNARTZ, Einführung in die chemische Physiologie, IVth. ed., p. 186.

may be markedly coloured by porphyrin. Sometimes cases of hydroa vacciniforme are found without porphyrinuria [7]). One case is known [8]) in which a clearly outlined gap made its appearance, punched out as it were, suggestive of scleromalacia perforans, in the sclera of both eyes, situated between the eyelids. It seems probable, in view of these cases being frequently associated with porphyrinuria, that here, too, there might be a disturbance of metabolism, in which necrosis is caused by toxic agents that are produced by the transformation of chemical substances under the influence of the rays.

The affection, designated as Xeroderma pigmentosum is distantly related to those discussed above. In this disease, which is often familial, pigmentations, tumours, and even veritable cancers may arise in all parts of the skin that are not covered by clothes. Generally speaking these tumours run a relatively benign course, they may however, although this occurs but rarely, metastasize to various parts of the body and by so doing entail death.

Fig. I and II show a patient affected with this disease. The entire skin of the face is covered with pigmentations and small tumours, whilst the nose presents a rather large tumour, which was found to be an epithelioma on microscopic examination. The man had a tumefaction in the posterior wall of the rhinopharynx, making swallowing difficult, whilst a paralysis of various cranial nerves suggested an affection of the base of the skull. The right eye presented a total paralysis of the oculomotor nerve. Fig. I shows the drooping of the right upper eyelid from paralysis of the levator palpebrae.

Fig. II shows dilatation of the pupil on account of a paralysis of the sphincter pupillae and outward deviation of the eye due to paralysis of ocular muscles. After patient had died insane, autopsy confirmed the diagnosis: metastasis of the cancer in the brain and at the base of the skull.

Fig. III shows cancer situated in normal brain tissue, fig. IV shows that the bone of the clivus blumenbachii and its surroundings were completely infiltrated by the carcinoma. The comparison of the effect of irradiation: of ergosterol in the body, of the eosin-pigs, of pregnant animals and of patients affected with hydroa vacciniforme, suggests that in xeroderma pigmentosum, chemical alterations due to irradiation cause pigmentation and formation of tumours. This approaches the theory advanced by Koegl and others of the close relationship existing between chemistry and malign tumours.

After this digression we will revert to our subject: the steroids. In the opening lines of HAMMERSTEN's [9]) chapter on steroids, we read: "As such, a class of substances is designated, of which cholesterol is the representative

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[7]) GARROD. Inborn factors in disease. Oxford 1941.

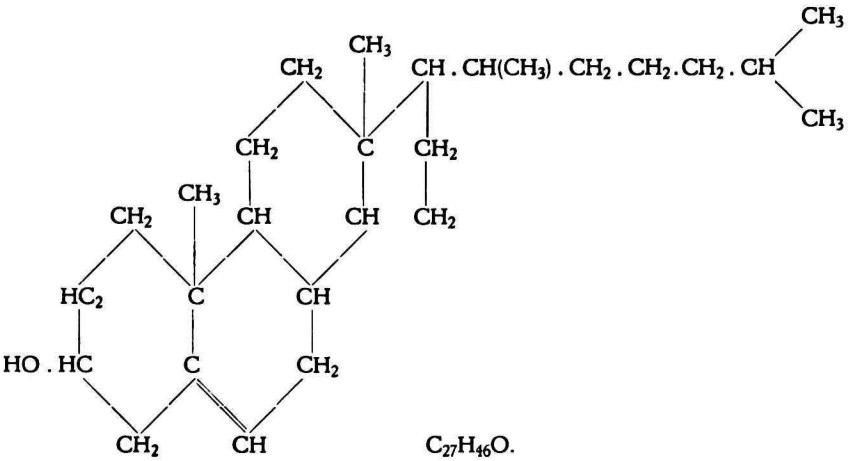
[8]) KUHNT. Über symmetrisch umschriebene Skleralnekrose bei Hydroa vacciniforme. Z. f. A. 1912, Vol. 27, p. 146.

[9]) L.c. 192.

that has been studied most and has been known for the greatest length of time".

Although we are not given a clear definition of the conception of "steroid", it nevertheless is encouraging as regards the facts that will be known of the main representative of this class, cholesterol. Our expectation is not realized, however, when further studying the subject. For in the next paragraph HAMMERSTEN observes: "The composition of cholesterol has not entirely been revealed as yet, it has however been studied very exhaustively by many investigators, notably MAUTHNER and SUIDA, WINDAUS, STEIN, DIELS with ABDERHALDEN."

When referring to this subject in the seventh edition of ABDERHALDEN, Textbook of Physiological Chemistry, which appeared in 1940, we again do not find a good definition of steroids, and read: "After laborious investigations one has succeeded in obtaining the following structural formula for cholesterin".



$C_{27}H_{46}O$.

It is evident, however, that not as much progress has been made in these twenty years as would appear, for ABDERHALDEN adds in a note: "It is not certain that this is the definite formula. Some authors assume that a closed chain consisting of seven parts is also present." In other words the structural formula of cholesterol was not as yet definitely known in 1940. Luckily above mentioned formule has become definite by the Röntgenanalyse of CARLISE and CROWFOOT [10]).

Cholesterol is an alcohol, therefore it is designated as a sterol in Anglo-Saxon countries, whereas the French and Germans use the word "cholesterin" and in our country attempts are being made to introduce the word "cholesterol".

Cholesterol is found everywhere in the body: in all body fluids, in the cells — it is one of the materials from which the cells are formed — but it is not known where it is situated in the cells; one author suggests that

[10]) C. H. CARLISLE and D. CROWFOOT, Proc. Royal Society **A 184**, 64 (1945).

it is situated in a scale-like structure round the cells. According to another it is within the cells. We are not sure how it enters the body; it may be absorbed from animal food by the intestine after it has been converted into esters, but it is an ascertained fact that it may arise within the body. A diet without steroids given for a long time cannot prevent cholesterol metabolism from being undisturbed, the amount of cholesterol may even increase.

Biochemists were greatly surprised by this cholesterol synthesis within the body. We will quote ABDERHALDEN once more: "The most surprising result of the investigations into cholesterolmetabolism is undoubtedly the finding that the animal organism is able to build up this compound. For many years it was thought that the animal organism was not capable of making ring structures" [11]).

Nothing at all is known, however, of the materials of which cholesterol is composed, how and where in the body it is made, is not known either. The adrenal glands have received consideration in this respect, but ABDERHALDEN says, and with reason: "We do not know anything about the materials effecting the synthesis of cholesterol, nor do we know which transformations take place and which tissues (resp. which organs) perform this synthesis, which is so interesting and important. At present all starting-points for an investigation in this direction are missing."

Cholesterol is found free in the body, and as esters with the three higher fatty acids (palmitic-, stearic-, and oleic acid). The amount in the blood serum is fairly constant viz. 1½ to 2 grammes; usually we assume 1,7 grammes per liter of serum. The ratio between free cholesterol and esters is in normal cases about 1½ or 2 to 1 in liver, skin and other tissues, in blood 1 to 1½ or 3, although great variations are possible. The liver controls the destribution of cholesterol but it is not known how. It is probable that not only is the absolute amount very important to man, but particularly the ratio of free cholesterol to esters.

The liver causes cholesterol to pass into the intestine, together with the bile, where it has a very significant function as far as nutrition is concerned. The cholesterol that is not required is absorbed again by the intestine; the remaining part is reduced to koprosterin by the contents of the large intestine and together with the faeces, it is discharged from the body.

It is highly probable that cholesterol has a very important function in the body, we are not certain, however, which function.

Summarizing we may conclude that, in spite of many investigations and the great advances made in this province, we know but very little of cholesterol. Some maintain it belongs to the lipoids, others disagree. The way in which and place of formation in the body is not known at all. However we are certain of the fact that it is an extremely important substance for the animal organism.

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[11]) L.c. page 47.

As we have seen above, definition and nomenclature of fats and lipoids are far from being perfect. The relation of fats to lipoids is not clearly outlined either. LEHNARTZ discusses in 1940 in his excellent textbook "Introduction to chemical Physiology", successively: fats, resins, phosphatides and cerebrosides, starting upon this last part with the opening lines." The fourth class of lipoids, the cerebrosides" etc. [12]).

So here he represents the fats as being a subgroup of the lipoids, which is not permissible in my opinion, because a fat cannot resemble a fat. In another passage of the same book [13]) LEHNARTZ says, when discussing the body fats: "Besides this part of the body fat, the depot fat, we find the organ fat, which does not consist of neutral fats for the greater part, but of lipoids". Here it is suggested that fats might partly consist of lipoids.

From this it becomes apparent that in spite of the great progress of biochemistry it is still far from being complete. We know comparatively little of so extremely important a substance as cholesterol, definitions and nomenclature of lipoids and fats are inadequate to such an extent as would make it advisable to revise this important matter which would greatly facilitate the study of these subjects, particularly for physicians who are but laymen in this branch of science and who are obliged to deal with lipoid diseases.

Although cholesterol is found throughout the body it is of special interest in the eye, for here cholesterol may be deposited in nearly all tissues in a manner observed by us: in cornea, aqueous humour, iris, lens, vitreous humour, retina etc., under pathologic conditions.

Disturbances of cholesterol metabolism may express themselves in various ways; when compared with the normal amount of cholesterol, there may be too much or too little cholesterol or the ratio of free cholesterol to its esters may be modified.

These three forms can be designated as hyper-, hypo- and dyslipoidosis cholesterica. Usually when examining for cholesterol, the quantity of cholesterol is most important, although it is very possible that dyslipoidosis cholesterica is much more important than hyperlipoidosis. Much attention was given to hypercholesteremia, especially when in the early part of this century CHAUFFARD and his school applied themselves to this subject. CHAUFFARD was of the opinion that in diseases of the kidney, the derivatives of urea, and cholesterol as well were prevented from leaving the body, which retention would give rise to azotemia and hypercholesteremia, and to the latter was attributed e.g. the occurrence of retinitis albuminurica. As the normal amount of cholesterol in the blood CHAUFFARD assumed 1.7 grammes (1.5—2 gm.) per liter of serum.

Subsequent investigators did not occupy themselves with hypercholesteremia as probably the disturbances that were supposedly due to

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[12]) LEHNARTZ: l.c. page 42.

[13]) LEHNARTZ: l.c. page 33.

it, were often found whilst the cholesterol content of blood was normal. It is not impossible that an investigation into the ratio free cholesterol-esters would have revealed deviations from the normal, which might partly or totally have accounted for the symptoms. Alternatively an increase of the cholesterol content may be found in the tissues and not in the body fluids.

An excess of cholesterol in the body may give rise to an increase of the amount of cholesterol in the blood, an increase of cholesterol in the tissues, or both.

Increase of cholesterol in the tissues may manifest itself in the deposit of crystals in the tissue, or in the appearance of granulation tissue with a high cholesterol content.

Free deposition of crystals in tissue we may often observe during life in the cornea, anterior chamber, lens, vitreous humour (forms of synchisis scintillans), retina etc.

A diffuse impregnation of the tissue with more cholesterol than is present in normal conditions, may give rise to formation of xanthomata, pseudo-tumours, which may be flat or elevated: xanthoma planum and xanthoma tuberosum. These vary in size from small swellings to large tumours, and often have a yellowish colour, hence the name of xanthoma; the colour is usually most clearly visible when the skin over the tumefaction is extended.

Xanthoma tuberosum is usually situated under the skin without infiltration of the latter. The xanthomata are mostly composed of lobes and closely linked up with tendons, sheaths or periosteum, especially in fingers, elbows, tibiae and ACHILLES tendon.

Xanthomata may be distributed throughout the body-xanthomatosis universalis; they are of most frequent occurrence in the eye lids and their surroundings, especially in the nasal canthus. This xanthoma is called xanthelasma and is situated in the skin, which seems to be atrophic.

Xanthomata occur on the eye lids a hundred times as frequently as they do on the other parts of the body, Xanthelasma is to be seen especially in patients suffering from liver diseases, diabetes, hypercholesteremia, but also in apparently normal persons. They may assume enormous dimensions in the eye lids as is shown by a publication of HARTMANN [14]), who observed a subcutaneous xanthoma the size of a pigeon's egg in each upper eye lid of a patient.

Xanthoma may occur as a hereditary affection, and thus in some cases it may be regarded as a constitutional affection.

Xanthomatosis is to be found as well in internal organs, usually in the bile ducts and the vascular system, especially in the coronary arteries, the valves of the heart and the intima of the aorta and other large vessels. It may be attended by arteriosclerosis and symptoms of cardiac diseases such

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[14]) K. HARTMANN. Klin. Monatsbl. f. Augenheilk. 1943, Vol. 109, page 555.

as affections of the valves and angina pectoris. According to ASCHOFF the arteriosclerotic process is heralded by infiltration of the intima of the aorta with cholesterol. LIEBIG and KOTTLORS are of opinion that arteriosclerosis and Xanthoma of the lids originate in the same underlying affection, viz. a cholesterol diathesis.

MÜLLER [15]) of Oslo describes various families where hereditary xanthomatosis associated with angina pectoris were found.

Besides lipoid granulations, consisting mainly of so-called foam cells or xanthoma cells, large swollen cells are also found in the xanthomata, containing much lipoid and also fat, therefore they are labeled "masses lipo-lipoidiques" by the French authors.

The fat is easily distinguished from the lipoids, fat stains black with osmium and red with Sudan III, lipoid stains gray with osmium and orange with Sudan III whilst moreover neutral fats have a single refraction and the lipoids produce a double refraction.

The amount of lipoid and fat is considerable, xanthoma deposits may contain about 25 percent of cholesterol and 20 percent of fat when dried.

Xanthomatosis may be attended by hypercholesteremia, though this is not necessarily the case.

Xanthomata are harmless in themselves, but by their localization they may be detrimental to vision and life.

The cornea may be impregnated with cholesterol crystals or masses of xanthoma to such an extent as to make the patients practically blind.

Fig. V shows that nearly the entire cornea is impregnated with cholesterol crystals, and only a small part of the pupil is left free. The patient's vision became worse and worse; in the stage shown in the illustration the acuity of that eye amounted to $1\frac{1}{2}/10$ with $+4 = 9—10/10$, but the crystals continued forcing their way, and so the eye resembled more and more the state of the patient's other eye (fig. VI) where the whole cornea has become one mass of crystals as it were, so that the vision was greatly reduced and in spite of the vision of the other eye still being good, complete blindness is impendent. Similar deposits of cholesterol crystals are to be found in dogs, mostly in the centre of the cornea [16]). Here the process is designated as lipomatosis of the cornea which is not entirely correct in my opinion, because fatty degeneration makes mention of only a part of the process and does not indicate the important part of deposition of cholesterol. In our patient hyper- and dyslipoidosis cholesterica exist, the total amount of cholesterol in the blood fluctuates from 200 to 334 (normally 170), the ratio of esters to free cholesterol is variable, e.g. 282 to 51, so $5\frac{1}{2}$ to 1 (normally $1\frac{1}{2}$ or 2 against 1).

[15]) C. MÜLLER. Angina pectoris and hereditary Xanthomatosis. Archives of internal Medicine 1939, Vol. 64, p. 675.

[16]) M. DREIFUSS. Symmetrische zentrale Hornhautverfettung beim Hund. Graefe's Archiv f. Ophthalm. Vol. 125, 1930, p. 67.

H. VEENENDAAL. Dystrophia corneae adiposa bij den hond. Tijdschr. v. Diergeneeskunde, Vol. 64, 1937, p. 913.

It is an appalling sight to see vision vanish completely without being able to do something about it.

It is true that in some cases a diet without steroids inhibits or retards the process, but this is not definite for as we know cholesterol of unknown origin can be built up within the body. Once the process has come to a stand-still cornea grafting may return some vision to such patients. In our case cornea grafting was done in both eyes with the result that the man had a visual acuity of 5/10, that he could do all his work and could drive an autocar.

Even more appalling may be the sight of the cornea being invaded by a mass of lipoid granulations, which, as fig. VII—XIII show, may give rise to blindness within a longer or shorter period, in this case in the course of some years. Here destruction of vision is even more effectual than in cases of crystal forming, when some acuity is usually left.

Fig. VII shows the picture of the cornea of a thirty years old man; part of the pupil is not involved as yet, acuity at that time, August 1921, still amounted to 4 or 5/10 following correction; in fig. VIII, June 1923, the pupil had disappeared almost completely and acuity amounted to 1/60, whilst (fig. IX) in March 1924, the cornea was almost entirely involved in the mass of granulation and acuity of that eye had completely disappeared.

Fig. X shows this patient's other eye, here lipoid infiltration starts at one spot of the cornea, attended with but few symptoms of inflammation. It completely resembles fatty degeneration of the cornea, and has often been labeled as such, but examination of parts of the mass that had been removed reveal the obviously lipoid character. Following correction in August 1921 vision amounted to 8 or 9/10.

Fig. XI shows that on November 14th. 1923, vision being 8 or 9/10, the original focus has extended and that temporally under it a new focus has formed quite independently, which in March 1924: vision being 6/10 (fig. XII) had fused with the first focus, because both had spread along the surface, whilst in September 1924 a small new focus, situated in front of the pupil, menaces the last free part of the pupil ($V = 1/10$). This spreading soon gave rise to complete blindness (fig. XIII).

Removed parts of the mass that had infiltrated the cornea consisted of granulation tissue, staining gray with osmium, and orange with Sudan III, which proved it to be cholesterol-containing tissue.

These lipoid focuses give rise to blindness here; when situated in other places they provoke severe morbid symptoms, they may even entail death when focuses in heart and vessels cause arterio-sclerosis, a disturbed function of the cardiac valves, angina pectoris.

Cholesterol may also be deposited at the base of the skull, e.g. round the hypophysis, as the metastatic carcinoma shown in fig. IV; this may give rise to hypophyseal manifestations such as diabetes insipidus, adiposo-genital dystrophy, sexual insufficiency etc.

All this leads us to a special form of lipoidosis cholesterica, the disease

that was described by HAND in 1893, by SCHÜLLER in Vienna in 1915 and by CHRISTIAN in America in 1919 independent of the others, therefore it is now called HAND–SCHÜLLER–CHRISTIAN disease. Afterwards it was recognized as being a lipoidosis. It is a syndrome, in which lipo-lipoid masses are deposited in several parts of the body: in the orbit, which gives rise to exophthalmus, round the pituitary body, resulting in the hypophyseal manifestations referred to above, under the skin of the skull, thus giving rise to the forming of lobate soft elevations, in the bones of the skull which leads to the formation of holes, punched out as it were, which are sometimes observed in great numbers.

The outstanding symptoms are: exophthalmus, holes in the skull, hypophyseal manifestations; in other places xanthomatous symptoms may be found as well in this disease. Not all symptoms of the syndrome have to be present simultaneously. The patient whose corneae are shown in the fig. VII—XIII presented, apart from these xanthomata corneae, an exophthalmus, and hypophyseal manifestations such as diabetes insipidus, adiposogenital dystrophy associated with a decreased libido. This makes us assume that here a diagnosis of lipoidosis cholesterica HAND–SCHÜLLER–CHRISTIAN should be established, although I do not know whether holes were present in the skull. The cholesterol proportions in the blood are not known either in this case.

In 1940 GRANCINI [17]) described a similar case in a nineteen years old girl, whose left eye had been removed three years previously in view of the diagnosis: malign tumour of the cornea. Unfortunately this eye had not been examined histologically.

The second eye presented an appearance greatly resembling our fig. VII, only in GRANCINI's case more formation of vessels was present. The removed parts of the mass, that infiltrated the cornea, were found to be granulation tissue containing fat and cholesterol with many xanthoma or foam cells, so that here again we are confronted with the typical "masse lipo-lipoidique" of the French authors. Besides the patient presented symptoms of diabetes insipidus and hypophyseal infantilism and therefore we are, in my opinion, justified in establishing a diagnosis of lipoidosis cholesterica HAND–SCHÜLLER–CHRISTIAN in both cases, whilst xanthoma corneae may be added to this disease as a symptom, though no holes were found in the skull and the total amount of cholesterol in the blood was normal. In this disease a vicious circle may be established; it is very probable that nearly all lipoidoses are subject to hormonal influence to a great extent, e.g. of the pituitary body. When, as in the disease under discussion, deposits round this organ cause the pituitary body to become diseased, the vicious circle is closed.

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[17]) L. E. GRANCINI. Di una rara osservazione di "adiposi primaria della cornea", insorta in ragazza affetta da infantilismo ipofisario e diabete insipido. Boll. Oculis. 19, 1940, p. 267.

The relation of HAND–SCHÜLLER–CHRISTIAN disease to lipoidosis cholesterica is often disputed, because hypercholesteremia is not found in all cases; it is possible that in these cases by means of an accurate determination of the ratio free cholesterol/ester a dyslipoidosis cholesterica may be found, in spite of a normal total amount of cholesterol in the blood. But even if this ratio is normal, tissue may deposit cholesterol, which is supplied by the blood in normal amounts. When evaluating the way via which an excess of cholesterol arises somewhere in the body, we are confronted with two great difficulties: 1. Examination of the amount of cholesterol in blood and tissue and for the ratio free cholesterol/esters is not so simple as to make the results reliable, and therefore we do not know for certain when a hyper-, hypo- or dyslipoidosis is concerned, even if we adhere to the following norms: a total amount of cholesterol in the blood of 1.7 (from 1.5 to 2) and a ratio esters/free cholesterol in blood of 1: from 1½ to 3 and in tissues such as skin and liver of from 1½ to 2 : 1. Therefore it is advisable to have the material examined in various laboratories so as to be able to compare the results and to allow a liberal margin when judging the question as to whether a deviation from the norm exists or not.

2. It is difficult to say where cholesterol, accumulated in the tissues, comes from.

In order to obtain accumulations of cholesterol and its esters in the body two factors are required:

Firstly: Cholesterol must be present in sufficient amount.

Secondly: The local tissues must be ready to store cholesterol, "hoard" it, one might say.

This readiness of the tissue may be of great importance, sometimes cholesterol is not deposited anywhere in the body tissues although the blood cholesterol content is very high.

SIEMENS designates this readiness of the tissue as cholesterinophilia, whereas POLANO calls it lipoidophilia.

POLANO has thus a wider conception of this idea and his designation comprises the readiness of the tissue in respect of other lipoids besides cholesterol alone.

SIEMENS and POLANO place great value upon the conception of the tissue being ready to receive cholesterol, whereas SCHAAF [18]) questions it. He does not deny the influence but in his opinion it is of minor importance when compared with the predominant influence of the amount of cholesterol the individual is supplied with.

As far as SIEMENS' view is concerned we have to admit, in my opinion, that this cholesterophilia may be of paramount importance. It is even imaginable that, the tissue having a great readiness, the latter is capable of withdrawing an amount of cholesterol, (the composition of the blood being

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[18]) SCHAAF, Experimentelle Beiträge zur Pathogenese der Xanthome.

normal), sufficiently large to permit cholesterol to be deposited in the tissues. It is even possible that the amount of cholesterol withdrawn from the blood by the ready tissues is so large as to cause the liver to fail in its function of regulation, thus giving rise to a hypocholesteremia in spite of, or rather on account of deposition of cholesterol in the tissues. These speculations provide another view of the relationship between xanthomata and cholesterol content of the blood. The readiness of the tissue to receive cholesterol and to keep it there may be increased when stimulating the tissue or impairing it. The amount of cholesterol in the blood may be greatly increased when a large quantity of food, containing cholesterol, is introduced into the intestinal tract. In this way VERSÉ obtained a cholesterol content in the blood of more than fifty times the initial value, when experimenting upon rabbits.

A modification of the cholesterol content of the blood may also be obtained by impairing the liver's regulating function by means of Roentgen-irradiation and intoxication by Phosphorus or other substances.

Accumulation of cholesterol in the tissue may also arise, apart from deposition from the blood, from degeneration of parts of the tissues, with a subsequent decrease of their own cholesterol content.

Fig. XIV shows a typical instance of xanthoma formation in the anterior chamber of a patient.

Thirty four years ago this patient was sent to me, because they were afraid that the white tumour, present in the chamber, might be a malign one, and might entail death the more so, as the growth was slowly increasing in size.

The child had been afflicted with congenital cataract, from birth for which an operation had been performed. As usually occurs remnants of the lens had been left in the anterior chamber. Indeed a whitish tumefaction was to be observed in the chamber, apparently hard, which on biomicroscopic examination, contained calcium and cholesterol crystals.

The eye was irritated to such an extent that I advised its removal, although I was convinced that we were not dealing here with a malign tumour, but with a pseudo-tumour due to the irritation, caused by the remnants of the lens.

On microscopic examination, as shown in fig. XIV, we see granulation tissue in the chamber with some giant cells and many fissures, clearly presenting the shape of the cholesterol crystals that had their site there.

It is not certain where this cholesterol come from, the blood, aqueous humour, adjacent tissue or degenerated lens tissue.

Deposits of cholesterol in the body may be studied with the aid of deviations from the standard found in man, such as the cases described above, where deposits existed in cornea and anterior chamber and by means of experiments on animals. Above we saw that xanthelasma is of far more frequent occurrence in man than xanthomata are in the remaining parts of the body, a sole deposit of cholesterol, however, is even more

frequently met with in man, it may be so frequent as to be regarded as a kind of physiologic symptom of old age, viz. arcus senilis corneae or gerontoxon corneae; this symptom is at the same time a fine example of cholesterophilia.

At 60 years of age arcus senilis is found in 63 % of all women, and 89 % of all men, thus in 75 per cent of all people. It is a reversible process, decreasing after the sixtieth year both in quantity and in intensity.

The arcus senilis begins as a gray arc at the upper edge of the cornea, covered by the upper eye lid; this is a place that is protected from external influences as much as possible; next, it begins in the lower part as well, after which both arcs may come together so as to form a gray-white ring, completely closed, and from 1 to 2 mm. wide (fig. XVI), which is situated a short distance from the limbus corneae and is separated from the latter by a narrow margin of corneal tissue, which is almost completely clear. Formerly arcus senilis was thought to be a fatty degeneration of corneal tissue. FUCHS regarded it as a hyaline degeneration until J. HERBERT PARSONS proved that here we have to do with a lipoid degeneration, viz. a deposit of cholesterol.

One would be justified in expecting that such a deposit could arise most easily in the limbus itself, in the neighbourhood of the vessels that transport cholesterol, the readiness of the tissue, however, cholesterophilia, decides the place of choice.

Where does this deposit come from? In my opinion it comes from the cholesterol, present at the site, due to changes in the tissue caused by old-age, but it is quite certain that an arcus senilis may also arise from hypercholesteremia.

A. VAN HERWAARDEN [19]) made some very interesting experiments on this subject in the laboratory of Prof. HERINGA. By means of feeding rabbits cholesterol he provoked a severe cholesteremia, which was so violent, that the cells in the cornea were clogged to such an extent as to be obstructed entirely. When trypan blue is injected into a vein of a normal rabbit, a zone in the cornea stains beautifully blue, a vital staining; when the same thing is done in a rabbit having hypercholesteremia this colour sometimes fails to make its appearance, the cells being so congested that there is no room left for the blue dye.

VAN HERWAARDEN has never seen an arcus senilis appearing spontaneously in his animals experimented, others have seen it, however. It is a matter of long duration; these experiments have to be continued for over two years in some cases. VAN HERWAARDEN tried to provoke the appearance of arcus senilis by stimulating or even impairing the tissue. He only succeeded in doing so by infecting the center of the cornea with Bacterium subtilis, then vessels entered the cornea and the arcus senilis followed the

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[19]) VAN HERWAARDEN. Academisch Proefschrift. Amsterdam 1937.

vessels. A typical example of the forming of a depot of cholesterol from the blood in hypercholesteremia.

When the hypercholesteremia in the limbus is of longer duration, cholesterol from the blood may pass into the tissue fluid and we get the experimental arcus senilis without vessels.

In the genuine gerontoxon of old age there are no vessels in the cornea and the depot will presumably arise from cholesterol that had already been present previously in the tissue.

The conclusive role the condition of the tissue plays becomes apparent from the fact that the extreme edge of the cornea, lying against the tissue that contains so much cholesterol, remains clear of cholesterol deposits, in spite of the vessels.

An enormously high cholesteremia may be provoked when feeding the animals much cholesterol.

VERSÉ [20]) fed rabbits on 5 percent cholesterol in linseed-oil.

At the outset of the experiments the cholesterol content in the serum amounted to 0.067 %, at the end of six days of cholesterol diet it amounted to 0.166, at the end of twenty days to 0.428; when the administration of cholesterol was stopped for eight days, the cholesterol content in the serum fell to 0.366, when cholesterol was given for another twelve days it rose to 0.716, after another eight days to. 0.92, one month after that it amounted to 1,4, and finally to 3.6, that is more than 53 times as much as at the outset of the experiment. In the course of many months VERSÉ succeeded in provoking an arcus senilis by means of such enormous doses of cholesterol. ENGELKING, CHUMA et al. succeeded in doing the same. This experimental form of arcus senilis differs, as regards its way of arising, from the one that normally occurs in man, for in the experimental form the supply via the blood is the cause of this lipoid deposit, whereas in the arcus of old age in man, there is probably a deposition of cholesterol from the degenerating tissue.

Although hypercholesteremia plays an important part in the experimental form, yet the influence of the readiness of the tissue should not be neglected, in view of the typical localization of the arcus in both forms.

Schaaf [21]) succeeded in obtaining a strong cholesteremia in his animals by giving them lanolin, a substance containing many esters of cholesterol together with free cholesterol and by damaging the liver at the same time, which controls the cholesterol content. The liver was impaired by means of injections of salversan, Roentgenirradiation of the liver, exposed by an operation, poisoning by toluylendiamine and combinations of these three methods. In his experiments that were continued for two years and

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[20]) M. VERSÉ. Zur Frage der Scheibeformige oder ringformige Hornhauttrübungen. Virchow's Archiv., 1924, 250.

[21]) FRITZ SCHAAF. Experimentelle Beiträge zur Pathogenese der Xanthome. Archiv f. Dermatologie und Syphilis 1937, Vol. 175, p. 279.

even longer, many changes were observed in the eyes, such as arcus senilis, other forms of cloudiness of the cornea, xanthomatous focuses in the ciliary body and in the sclera, turbid conditions of the vitreous humour, whilst the background of the eye could resemble the surface of broken crystals.

The most interesting factor, as far as our subject is concerned, at the present moment, is that the sclera presents xanthomatous alterations as well in a similar hypercholesteremia.

In the eyes of animals, in which hypercholesteremia had been provoked by POLANO M.D. and SNELLEN M.D., the ophthalmologist PIECK working in our laboratory, on several occasions found important manifestations in the sclera, in the shape of circumscribed hyaline-like masses surrounded by a lymphocytic reaction.

As we have seen above, many alterations of the eye may occur, when cholesterol metabolism is disturbed either experimentally or spontaneously, such as xanthelasmata, crystalline deposits in the cornea and the fundus, lipoid degeneration of the cornea, xanthoma in the anterior chamber of the eye, cornea and sclera. We will now revert to

SCLEROMALACIA PERFORANS
CASEHISTORIES.

1) The first case of this disease, which I saw, was shown to me by Dr. VAN HOORN, Ophthalmologist, the Hague, in 1928. The patient was a fifty-five years old woman, suffering for many years from a chronic affection of the joints, which did not allow her to move around freely. The joints were swollen, and many of them were completely ankylotic.

For many years her vision had been deteriorating and when I examined her for the first time she was almost blind.

The cornea presented deep and superficial cloudiness, especially at the periphery, and many crystals were present in the cornea. Not much was to be seen of the iris, it seemed to be atrophic, both lenses presented cataracts almost mature, residues of an iridocyclitis were present. All this had impaired acuity to so great an extent as to result in the right eye having a perception of light with a good projection and the left eye a vision of 1/300.

The sclera had been impaired most, for there a great number of small and large holes were present, the larger apparently having arisen from a confluence of smaller ones (fig. XV). Over the holes the conjunctiva was in a very bad condition, it was atrophic, covered some holes entirely, others not at all, mostly only frays were left. The uvea was exposed more or less in the holes, but did not protrude.

In the Hague the diagnosis of this affection had been established as gout, so that I thought the crystals that were visible in the cornea might be crystals of urate and I considered scleromalacia perforans urica as a name for this disease. From the very beginning, this affection of the sclera

was not regarded as a local one and at once investigations were made into a possible relation with a generalized affection.

Examination in the Internal Clinic of Leyden University (Director Prof. W. A. KUENEN) revealed that this was not a case of gout but of chronic articular rheumatism. Manifestations of lues or tuberculosis were not found.

Dr. VAN HOORN told me, that, prior to the formation of a hole a yellowish soft little lump arose below the level of the conjunctiva resembling an abscess. When it was opened no pus, but a mass consisting of yellowish granules appeared. Unfortunately this mass had never been examined. In order to prevent infection I covered all holes with labial mucous membrane, which grew very well, and no infection occurred in the eyes.

A cataract extraction performed by me upon the right eye slightly improved acuity, the part of the iris that had been removed, revealed atrophic changes only, on microscopic examination; small parts of the sclera removed during operation revealed degeneration with but few manifestations of a probably secondary inflammation.

Some years afterwards the patient died, autopsy was not performed, and an eye could not be secured for examination.

Epicrisis: Female of fifty five years old, affected with chronic articular rheumatism, holes in the sclera, atrophic conjunctiva and iris, opaque cornea with crystals, residues of iridocyclitis, little, if any, inflammation.

Diagnosis: Scleromalacia perforans, chronic articular rheumatism (arthritis deformans).

II. On March 11. 1931 a sixty-eight years old man was sent to me by his physician, because the patient had been seeing a "fly" in front of his right eye for some days.

The man told me that forty-eight years ago he had had an inflammation of the eyes, his eyes had been red and painful and that this had recurred many times. It did not seem to have been very severe, for he had never taken the trouble of consulting a doctor.

He was aware of the fact that for many years he had a black lump in his left eye, that had gradually been growing, and, although he was living a few kilometers from our clinic, he had never consulted a doctor nor gone to the clinic to have this lump examined.

The results of our examination were remarkable indeed. Neither eye showed signs of irritation, their tension was normal. Vision of the right eye $=$ 6/10, with Cyl. $+$ 2 axis 60° temporally $=$ 9/10. Vision of the left eye $=$ 2/10 with cyl. $+$ 2 axis 45° nasally $=$ 4/10. Fundus oculorum normal, apart from some "drusen". The cornea of the left eye (fig. XVII) was slightly opaque in the periphery and presented a very thick arcus senilis. In the upper part of the cornea a great mass of crystals was visible, and when examined with the corneal-microscope and slit lamp it gave the impression of consisting of urate crystals.

Just over the cornea a black mass was to be found, partially overlapping

the cornea, which turned out to be a prolapse of the iris, protruding from a narrow slit in the sclera near the limbus corneae (fig. XVII). The prolapse was entirely covered by the very thin conjunctiva.

In the right eye (fig. XVI) the periphery of the cornea was somewhat brighter, the arcus senilis, though not so thick as that in the left eye, was much heavier than normal and was composed of the same crystals. On the nasal side of the cornea a subconjunctival cyst was observed, resembling the picture of a strongly filtrating scar, following a LAGRANGE or ELLIOTT operation; this is the prototype of a cystous scar indeed. Through the semitransparent cyst a narrow vertical slit in the sclera was observed.

As far as he knew the man had never experienced any trauma to his eyes and thus spontaneous perforation of the sclera was established as the diagnosis.

Some months later the conjunctiva over the prolapse began to become atrophic, the iris was exposed and infection was feared. On 11. June 1931 I removed the atrophic conjunctiva, freed the prolapse of the iris, excised it, extirpated a small piece of corneal tissue containing crystals and covered the wound with solid conjunctiva, taken from the neighbourhood. Recovery was uneventful. The fluid was removed from the cyst of the right eye by means of aspiration, the cyst turned out to be multilocular, the aqueous humour did not drain, the cysts filled again and within a few days they had regained their previous shape.

Microscopic and chemical examination proved the crystals not to be urate, but cholesterol crystals [22]).

Ten years afterwards, in March 1941, the condition of the eyes had practically remained the same, arcus senilis and mass of crystals in the cornea having increased rather than decreased. In view of the arcus senilis decreasing rather than increasing after the sixtieth year in normal cases, I thought that in this case a disturbance of cholesterol metabolism, i.e. lipoidosis cholesterica, might exist in this man, who was then seventy-eight years of age.

Repeated examination of the blood, revealed a total amount of cholesterol ranging from 175 to 290 mgm. per cent, free cholesterol being 44.9 mgm. per cent = 15.5 per cent of total cholesterol, esters begin 245 mgm. per cent = 84.5 per cent of the total amount; proportion esters to free cholesterol being 5.45 to 1.

So here an abnormal ratio between esters and free cholesterol existed and we are justified in speaking of dyslipoidosis cholesterica, whilst the total amount of cholesterol was fluctuating from "normal" to "increased".

When exhaustively examined in the Clinic of Internal Medicine manifestions of rheumatism, gout, lues or tuberculosis could not be found in this patient.

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[22]) So in the cornea the same affection existed as ZEEMAN described as lipoidosis cornea. 1947, Geneeskundige bladen, 41e reeks, XII.

Epicrisis: Old man, having had from childhood a small perforation of the sclera in each eye, situated in the intercalary párt of the sclera, and through which aqueous humour or iris appeared. No rheumatism, gout, lues or tuberculosis. Dyslipoidosis cholesterica did exist however.

Diagnosis: Scleromalacia perforans that made its appearance when patient was young. Dyslipoidosis cholesterica.

III. Patient O.

Patient knows that for many years he has had a small black lump in his right eye, vision of which is good. In the Indies he was affected with lues, associated with iritis of both eyes. His left eye is much worse than his right one.

Patient had no complaints as regards his eyes, but, when he happened to come to the Ophthalmologic Clinic in 1934, accompanying his son (case IIIa), he asked me to have a look at his right eye, which had presented a black lump for at least seventeen years, and had attracted his attention for the first time when he was nineteen years of age, although he was not able to tell whether it had been there before. Patient was thirty-nine years of age when I saw him.

Results of the examination: Vision of the right eye was found to be 2/10, with cyl. — 4 axis vertically sph. + 1 = 12/10. Visual acuity of the left eye = 1/10, with —4 = 5/10.

In the right eye, quite close to the limbus, at about thirty degrees, a black, uneven prolapse of the iris is visible in the sclera (fig. XVIII), that has almost forced its way through the conjunctiva covering it, the pupil has been drawn upward to a certain extent, it responsed readily, a great amount of pigment is to be seen on the capsule of the lens, the lens is clear, the fundus normal, various posterior synechiae exist.

At first glance this affection seemed to be unilateral, but on closer examination the left eye presents a small gray spot, symmetrical with the perforation of the sclera of the right eye (fig. XIX), the sclera is thin here, and when examined with the slit lamp it is obvious that the interior layers of the sclera are missing. The pupil is narrow and irregular, an occlusion of the pupil with old posterior synechiae exists, whilst in the fundus FUCHS' coloboma is met with.

Symptoms of gout, rheumatism or tuberculosis are not found. Patient is now kept under regular observation in order to excise the conjunctiva over the prolapse, should it become more atrophic, and to cover the whole with mucous membrane. So far the situation is all but stationary, as well as case Number II, which proves how slowly this process may run its course.

WASSERMANN's reaction is negative in the blood, cholesterolcontent is fairly high, the ratio between esters and free cholesterol is abnormal.

Total cholesterol 265 mgm. per cent, free cholesterol 42.3 mgm. per cent, that is 16 per cent, esters being 222 mgm. per cent = 84 per cent of the total amount. Ratio free cholesterol and esters = 1. : 5¼.

Epicrisis. Man, about forty years of age, having a perforation in the intercalary part of the sclera from his twenty-second year at least, whilst in the other eye the interior layers of the sclera are missing in a small spot, symmetrically situated with respect to the defect in the former eye.

Diagnosis: Scleromalacia perforans, prolapse of the iris, hyper- and dyslipoidosis cholesterica. Lues.

Case IIIa. Patient O. born November 12. 1923, son of patient III. On 14. July 1931 patient was referred to us by his doctor on account of an outward deviation of the left eye, vision of which was poor.

The right eye is entirely normal. Visual acuity = 10/10, refraction hypermetropia 1 D.

Apart from an outward deviation of 15 degrees the outer aspect of the left eye is normal; in the fundus oculi however, we observe in the region of the macula, a lump, having a yellow colour, containing some pigment, about the size of a papil, presenting a round opening, situated nearly centrally, from which a white crystalline mass is protruding (fig. XX).

A white crystalline mass seems to be present here, covered by the retina, the red colour of the fundus is unable to shine through the retina on account of this mass, and thus the yellow colour of the macula lutea [23]) is shown to full advantage, except for the place where the crystalline mass has broken through the retina so as to make the white crystals visible. It is possible that these crystals are cholesterol and, underneath, the sclera may have degenerated.

This condition remained almost stationary, the hole in the retina increased in size, however, and so did the crystalline mass, protruding from it.

Examination for cholesterol revealed in the blood: total cholesterol 250 mgm. per cent, free 33.9 mgm. per cent = 13½ per cent; esters 216.1 mgm. per cent = 86½ per cent, thus ratio between free cholesterol and esters = 1 : 6½. So the son also has a slight hyperlipoidosis and an obvious dyslipoidosis cholesterica, as has his father, who is suffering from scleromalacia perforans.

Epicrisis: Son of patient III. In an eight-year-old child a crystalline mass (Cholesterol?) was found in the macula of one eye behind the retina, partially perforating the latter, and afterwards a disturbance of the lipoid metabolism was revealed.

Diagnosis: Dyslipoidosis cholesterica. Scleromalacia perforans posterior? May be a hereditary dyslipoidosis cholesterica is present here, attended by different manifestations in the eyes of father and son.

That the yellow colour of the macula lutea becomes perceivable when an impediment prevented the red colour of the fundus from overshading the yellow one, was likewise observed by me in a case of a tumour for-

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[23]) J. VAN DER HOEVE, Die Farbe der Makula lutea. Von Graefe's Arch. f. Ophthalmologie, Vol. LXXX, 1, 1911, p. 132.

mation in the fundus oculi in Recklinghausens's disease, where a tiny tumour in the macula distinctly presents the yellow colour [24]).

IV. Female, 66 years of age. This patient was shown to me by the ophthalmologists HARDERS and VAN HAEREN at Rotterdam in 1940. For seventeen years she had been suffering from rheumatism, affecting several joints, resulting in atrophy of the surrounding parts, besides deformities and contractures.

Patient is afflicted with nephritis as well. For some years she has had slight ocular complaints affecting both eyes. Both eyes, on first ophthalmologic examination, presented many and large defects in the sclera, covered with little, if any, conjunctiva, extending from near the cornea to far beyond the equator (fig. XXI), some of these gaps are separated by such narrow strips of sclera as to give the impression of being about to fuse.

On the right side a strong exophthalmus existed, the conjunctiva of both eyes was injected.

In the right eye an infection had made its appearance, giving rise to a panophthalmitis in view of which this eye was enucleated on 17. May 1940.

In order to prevent a similar infection of the left eye the afore-mentioned ophthalmologists covered the uvea exposed in the openings of the sclera with labial and buccal mucous membrane along with a firm layer of fat on 29. May 1940. Recovery of all this was uneventful, but, as the flap retracted somewhat and the defect extended, we together performed a similar grafting on July 3. 1940, which covered the defects sufficiently, and no infection occurred in the eye up to the time of patient's sudden death on 17. February 1941, whilst the visual acuity remained constantly 6/8.

Cholesterol content of the blood was determined but once and was found to be 135 mgm. per cent, so it was rather low, though one would not be justified in designating it as a hypolipoidosis. Unfortunately the blood was not examined for free cholesterol and esters.

Symptoms of gout, lues or tuberculosis were not found. A post-mortem could not be performed, nor could the left eye be obtained for examination.

Morbid anatomical examination of the enucleated right eye yielded the following result.

Only a small portion of normal sclera was to be observed in the entire eye ball. In some places the remnants of the sclera had become necrobiotic to necrotic. Necrotic parts of the sclera were surrounded by an infiltrate, consisting of white cells, lymphocytes and a few giant cells (the type of foreign body giant cells); they behave like sequesters, as it were, that are going to be expelled by an inflammatory reaction. The sclera contained an infiltrate in many places, mainly composed of white cells, in other places the sclera seemed to have changed into fatty tissue, numerous capillaries and larger vessels were found here as well. The cavities, in the sclera

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[24]) Vide illustration in Graefe's Archiv 1923, Vol. 111, p. 14 and in Kurzes Handbuch der Ophthalmologie, Vol. V., p. 614, fig. 175.

resulting from the dissolution of larger pieces, are filled, especially at the anterior side of the eye, by a sanguineous granulation tissue, covered with epithelium in a very irregular manner. The epithelium often grows deeply into the defects, in the form of a sprout.

In one spot, near the equator of the eye, a very large defect had made its appearance, from which the contents of the eye: retina, chorioid, aqueous humour, were protruding. The space of the vitreous humour was filled by one large mass of pus. The choroid had become tremendously thick, had been infiltrated with lymphocytes and was partly detached from the sclera, the lamina fusca had fallen apart into membranes containing serous fluid, pigment and exudate. Iris and ciliary body were in a condition of violent purulent inflammation.

The lens was cataractous and backwardly dislocated, pulling the iris with it, so as to make the anterior chamber very deep. The retina was completely detached and was atrophic and so was the optic nerve. The papilla was infiltrated with lymphocytes, and some lymphocytes were to be found in the sheaths of the optic nerve.

Epicrisis: Female, sixty-six years of age, suffering from chronic rheumatism for seventeen years, defects in both sclerae, panophthalmitis of the right eye. Nephritis.

Diagnosis: Scleromalacia perforans and panophthalmitis. Chronic articular rheumatism (arthritis deformans). Nephritis.

V. A sixty-one years old man came to the Ophthalmologic Polyclinic of Leyden on 15. March 1940, stating that, ever since 1938, he had had troubles with his eyes, especially on the left side, and complaining of photophobia, tears and burning.

For eight years he has been afflicted with chronic articular rheumatism. In 1938 he was treated in the University-Clinic of Amsterdam, where a diagnosis of scleromalacia perforans was made. Professor ZEEMAN was so kind as to supply me with the following information.

„Patient P. H. H. came to the polyclinic of the Wilhelmina Hospital in December 1938 for the first time, the left eye being principally affected: scleromalacia perforans, marginal alterations of the cornea, some of them almost holes, some small infiltrates in the cornea and on the left keratic precipitates.

Visual acuity, following correction, was ½ for the right eye, and for the left eye 1. In September 1937 patient had been seen in the polyclinic of the Onze Lieve Vrouwe Hospital and treated with atophan and colchicine for chronic gout, so that in September 1938 his "gout and rheumatic symptoms were much less severe".

In view of the patient appearing to have internal disturbances (in the polyclinic patient was found to look cyanotic) he was referred to the polyclinic for Internal Diseases, and was admitted to the ward of Professor SNAPPER.

As major disturbances were noted:

1. Affections of the eyes.
2. Symptoms of an exudate in the left posterior lower part of the thorax (March 1939).
3. A hissing diastolic souffle of the heart that afterwards disappeared.
4. Enlargement of the liver and probably of the spleen, left kidney palpable.
5. Rheumatoid findings on arms and legs, associated with nodules at the extensor side of the joints.

27/2. In the evening suffocative attack; electrocardiogram showed a typical coronary thrombosis. No pericardial friction sound.

1/3. Pericardial friction sound in a few places, disappearing again after some days.

14/4. Electrocardiogram reveals an obvious improvement.

18/4. Temperature considerably elevated. Physical examination: same findings as before.

2/5. Physical findings in the lungs are less, but have not as yet quite disappeared. In the abdomen the enlarged liver is still palpable, spleen and kidney are not.

8/5. Biopsy of a small part from near a joint. Report of Morbid Anatomist: the picture corresponds with juxta-articular nodosity, connective tissue poor in cells, hyaline connective tissue for the greater part in which large and small areas of fibrinoid necrosis are to be found, sometimes cavities are formed. At the margin of the necrosis, in which some remnants of nuclei are occasionally met with, the fibroblasts have been arranged in a radiating manner; sometimes giant cells may be found as well in this area. Outside the tumour loose connective tissue and some fatty tissue, in which small vessels are found surrounded by parvicellular infiltration.

Blood: March 1939: Serum cholesterol 161 mgm. per cent."

As a pre-stage of the gaps in the sclera yellowish and gray subconjunctival soft elevations were observed, similar to those in the case I of Dr. VAN HOORN, of which the figures XXII and XXIII, for which I am indebted to Professor ZEEMAN, give a clear picture.

March 15. 1940 we found in this man:

Visual acuity of the right eye = 1/10 with + 3 = 4/10; V.O.S. = 1.5/10 r. with cyl. + 1.5, 25° nas, sph + 2.5 = 3 — 4/10 f.

Apart from defects in the sclera larger and smaller initial foci were found in the right eye, having a grayish and yellowish colour, as is shown in fig. XXII and XXIII.

Nasally in the limbus the left eye presented a defect in the sclera that had all but perforated; above the cornea the sclera has completely disappeared in the region of the equator and the uvea lies bare in the gap that extended to the size shown by fig. XXIV, shortly before his death on July 6.

Both eyes presented the residues of iridocyclitis, the vessels in the fundus are narrow and produce the impression of being sclerotic.

Patient was admitted to the Academic Hospital of Leyden, April 22. 1940, where he stayed until his death, caused by a cardiac failure on the 6th. of July, after having been in the Ophthalmologic ward and then in the Department of Internal Medicine.

During these months the defect in the sclera extended in two ways, viz. by extension of the gaps and by the arising of new yellowish-gray nodules under the conjunctiva.

Some of these were removed; they consisted partly of a soft, granular mass, partly of hard yellow tissue. On morbid anatomical examination they were found to consist of granulation tissue containing much cholesterol, partly hyaline connective tissue, in which areas of fibrinoid necrotic zones with the formation of cavities and giant cells were found; this was quite the same as had been found in the nodules near the joints when examined at Amsterdam. In this case the process in the sclera could be followed from the onset of new yellowish-gray foci to the end, the total defect, covering a great part of the sclera, clinically as well as anatomically.

On removal of some of the subconjunctival nodules the uvea was found to be shining through it with a gray colour, and so the formation of defects in the sclera turned out to be far advanced, without it being possible to tell whether the debris, found in the nodule, were the rests of the sclera, becoming primarily necrotic, or, that the process in the subconjunctiva was primary, and secondarily dissolved the sclera; in all probability both processes are due mainly to the same internal cause.

When taking an accurate life-history the patient is found to have had slight eye complaints, when he was about twenty years of age, these expressing themselves principally in pricklike pains during the night.

Swelling of the left hand, afterwards swelling of other joints, constituted the onset of his rheumatic complaints in 1933, he had been treated for them repeatedly with ultraviolet rays, injections, cure in Oeynhausen etc.

The patient had had various diseases before, and had been operated for a duodenal ulcer, inguinal hernia, prolapse of the anus, varices. Now patient presented nodules on the tendons of the flexors of the hands, on his fore-arms, elbows, and knees; acne rosacea, a commening rhinophyma, exudative pleuritis, dilatation of the heart to either side, systolic souffle at the apex.

In the pleural fluid 448 mgm. per cent of cholesterol was found, later this increased to 664 mgm. per cent and contained cholesterol crystals. In spite of this high cholesterol content the total amount of cholesterol in the blood was normal, ranging from 160 to 180. It has been repeatedly examined, both here and in Amsterdam.

Examination for gout, tuberculosis and lues gave negative results.

Clinical diagnosis was: primary chronic rheumatism, scleromalacia perforans. Pleuritis exsudativa sinistra. Insufficientia cordis, embolus?

Morbid anatomical examination revealed: pericarditis serofibrinosa et proliferativa (adhaesiva). Pleuritis fibrosa adhaesiva dextra et sinistra. Hydrothorax dextra (600 ccm.) et sinistra (100 ccm.). Perisplenitis fibrosa adhaesiva. Cyanosis hepatis et renum. Cyanosis et induratio lienis. Arteriosclerosis incipiens renum. Arthritis chronica (rheumatica). Oedema cruris dextri. Scleromalacia. Arteriosclerosis et atheromatosis art. aortae.

Cicatrix ulceris duodeni.

In the blood 200 mgm. per cent cholesterol was found, ratio between free cholesterol and esters 1 : 1.2, in normal cases this is 1 : 1.5 to 2; so here we have to deal with a slight dyslipoidosis cholesterica in the blood, which proves to be much higher when examining parts of the tissue.

Tissue of the liver and of a subcutaneous nodule of the right arm had been examined: in normal cases the ratio between free cholesterol and esters is the same in either tissue, in this case, however, it was very different, viz. in the subcutaneous nodule 1 : 1.65, in the liver 6.06 : 1 = 1 : 0.165, so the proportionate number in the liver was ten times as large, as regards free cholesterol, as it was in the nodule. Although in both tissues the total cholesterol content in the dry substance was far from normal (normally in the liver it is 0.9—1.3 per cent, in our patient 1.13 per cent; in subcutaneous tissue it is, in normal cases 0.7—0.8 per cent of the dry substance, and in our patient it was 0.82), the ratio between free cholesterol and esters proved that here we were dealing with a severe dyslipoidosis cholesterica.

Microscopic examination revealed deviations from the norm in numerous organs:

Kidney: Arteriosclerosis with centres of increase of connective tissue, congestion.

Spleen: Proliferative perisplenitis.

Liver: Moderate dissociation of liver cells, slight albuminous degeneration with fatty degeneration of the liver cells, hemorrhagic centres.

Pericard: Fibrinocellular, partly proliferative, pericarditis.

Aorta: Intima partly absent, partly a pink mass without any structure, deposits of calciumsalts.

Coronary arteries: atheromatosis, lime, double-refractive cholesterol crystals and fat in the intima, so a lipo-lipoid mass.

Elbow: Proliferative-cellular periarthritis. Myositis-arteriitis.

Subcutaneous tissue: Rheumatic inflammation attended with necrosis and deposits of cholesterol crystals, a moderate amount of fat, "masse lipo-lipoidique".

Heartmuscle: Arteriosclerosis; strong proliferation of connective tissues.

Mitral valve: fibrosis.

Papillary muscle: severe fibrosis.

In the pericardia fluid total cholesterol 200 mgm. per cent, ratio free cholesterol and esters 1: 1, 2.

Morbid anatomical examination of one of the eyes revealed: (Fig. XXV

and XXVI). Enormous defect in the sclera from the region of the limbus to near the equator. The remaining part of the sclera is in a condition of necrobiosis or necrosis. Parts of the sclera do not stain at all or only very poorly, between them fibrils are often found that stain well, therefore the whole produces a frayed appearance. In other places evenly stained pieces of sclera are found without any structure, like a kind of sequestrum surrounded by necrobiotic fibrils of the sclera. Further foreignbody giant cells are found and newly formed capillaries and slight hemorrhages. This produces the impression that a part of necrotic tissue is about to be expelled, thus resulting in a defect. In this defect irregularly infiltrated granulation tissue is formed immediately; an irregular mass of epithelium has partly covered and invaded it with an infiltrate of lymphocytes, leucocytes and an occasional plasma cell. A similar infiltration, but with many more plasma cells, is met with in the periphery of the choroid, and the lamina fusca has become a mass of pigmented membranes.

The ciliary body at the site of the defect in the sclera presents but little of its normal muscular structure, it is greatly hyperemic and infiltrated, part of the processes show an amyloid degeneration.

Epicrisis: Man, 61 years of age, with slight eye complaints since his twentieth year, after the fifty-third year rheumatism, pleuritis with much cholesterol in the exudate, arteriosclerosis, aortae et arteriae coronariae, enlarged liver.

Scleromalacia perforans, sudden death on account of cardiac failure.

Diagnosis: chronic rheumatism, scleromalacia perforans, dyslipoidosis cholesterica.

When summarizing these five cases, we find a spontaneous defect-forming in the sclera, resulting in a complete perforation in nine eyes, whilst in one eye only, the interior layers have disapperared in a small area.

Three of the patients presented chronic articular affections, resulting in an ankylosis of the joints, so that in two of them (I and IV) we might even speak of an arthritis deformans. Two of our patients (II and III) were entirely free from rheumatic affections.

In three cases (II, III and V) in which the proportions of cholesterol were closely examined in the serum, and sometimes in the tissues as well, a considerable deviation from the standard was found in the ratio between free cholesterol and esters, that is a dyslipoidosis cholesterica, irrespective of the total cholesterol content of the serum being normal or not.

When trying to construct the clinical picture of scleromalacia with the aid of these cases, we may say:

Scleromalacia is a syndrome, outstanding symptoms of which are:

1. the appearance of holes in the sclera;
2. articular affections;
3. dyslipoidosis cholesterica.

Accessory symptoms are: degeneration of the conjunctive, arcus senilis, deposition of crystals in the cornea, necrosis in the bones, affections of the

kidneys, pleuritis with an exudate abundant in cholesterol, arteriosclerosis arteriae aortae et coronariae, with cholesterol deposits in intima, affections of the liver, etc.

Both in case Number V and in MYLIUS' [25]) case nearly all organs in the body were involved.

Complications: As such were found iridocyclitis, severe infection in the form of an iritis with much hypopyon (Rochat) or panophthalmitis (case number IV).

Sequels: Formation of cysts, prolapse of the iris, cataract, ankylosis of the joints, cardiac failure.

Age: ranges from twenty to sixty years.

Sex: Neither sex seems to predominate.

Morbid Anatomy: In the first stage soft or hard nodules were found in the eyes, having a yellow or gray colour, which, on anatomical examination, proved to contain hyaline connective tissue, in which areas with fibrinoid necrosis, appeared and where cavities were formed as well as giant cells, and granulation tissue with fat and cholesterol. Therefore they may be regarded as xanthomata subconjunctivales or episclerales. In the second stage local liquefaction of the sclera is complete and a gap has made its appearance, in which we find a central necrosis surrounded by a broad wall of granulation tissue, which is abundant in vessels, with nests of leucocytes and giant cells, necrotic and necrobiotic scleral fibrils, which are sometimes walled off or expelled like sequestora, whilst the epithelium tries to cover everything and to grow in everywhere. MYLIUS' observation corresponded entirely with ours in this respect.

In the body MYLIUS found nodules in nearly all the organs ranging in size from a miliary tubercle to infiltrates of a few square centimeters. All these nodules resembled each other as regards their quality. The alterations of heart and joints, are most striking, but in nearly all other organs similar alterations were present abundantly as well.

In our case V, too, we saw how in many organs alterations were met with, corresponding with these and how lipo-lipoid masses were found in the walls of aorta and the coronary artery, so that we are justified in speaking of xanthoma-formation here.

Etiology: unknown so far, it is an ascertained fact however, that gout, tuberculosis and lues do not play a part.

Course of the disease and pathogenesis: The process is very chronic and may cover many years. The affection of the eyes commences with the appearance of small yellow-gray subconjunctival or episcleral elevations, more or less solid, when they are opened a yellowish "porridge" appears, though they may consist of a more solid lump.

Afterwards defects in the sclera make their appearance, which may be solitary or occur in great numbers, they may extend by fusing with other defects or their borders may spread. In either case few, if any, inflammatory

[25]) K. MYLIUS, Rheumatismus und Auge, Der Rheumatismus, Vol. 22, p. 76.

symptoms are observed. When the gaps are situated in the intercalary part of the sclera the anterior chamber contents: aqueous humour or iris, may protrude. This state of prolapse of the iris, and subconjunctival cyst may exist for over forty years.

When the perforation is situated in posterior regions, ciliary body or chorioid may appear in the opening, these tissues usually do not protrude. Wherever the hole may be situated, an infection may occur at any time, if it is a mild form, an iridocyclitis arises, with all consequences contingent upon it, if it is a severe one an iritis arises with hypopyon or panophthalmitis.

The destruction of the sclera may assume enormous dimensions, the greater part of the sclera may even disappear.

It is a noteworthy fact that so far, the smallest openings in the sclera were only found in the intercalary part. It is possible that this is due to the fact that small openings that are situated in posterior regions, are not easily found, whereas even the smallest gaps in the intercalary part become obvious, because the contents of the eye protrude. There is also a possibility of ocular tension playing a role here, that the degeneration of the sclera is more easily effected in normal ocular tension, whilst the sclera offers a greater resistance when the ocular tension has decreased on account of a fistula in front.

Up to the present in many countries, cases are known, having gaps in the sclera in front of the equator, caused by scleromalacia, and only a few of them extend behind the equator; it is possible, however, that behind the equator they are just as numerous, but that they do not provoke symptoms there.

Frequently scleromalacia is attended by an articular affection sometimes of a very severe character, even arthritis deformans may result.

It is remarkable that the cases of scleromalacia without articular involvement that have been observed up till now were localized in the intercalary part (II and III) or, at any rate, quite close to the cornea (WOJNO) [26].

The articular affection is mostly noted earlier than scleromalacia is.

As with all syndromes not all cardinal symptoms have to coexist.

It is possible that the cardinal symptoms are interrelated etiologically.

It is almost unimaginable that scleromalacia would be the cause of the articular affections, and also the reverse etiologic relationship is very unlikely.

As far as lipoidosis cholesterica is concerned things are entirely different. By giving rise to xanthomatous disturbances in the sclera and in the joints lipoidosis cholesterica may be held responsible both for the appearance of defects in the sclera and for the articular affection, whilst furthermore a great part of the other symptoms, such as pleuritis with an exudate

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[26]) S. WOJNO. Traité d'Ophthalmologie, T. IV, p. 866.

containing many cholesterol crystals, arteriosclerosis aortae et coronariae with cholesterol-containing tissue in the walls, and renal involvement may also be explained by it. As lipoidosis cholesterica, scleromalacia is to be grouped with the xanthomatoses. Scleromalacia bears the closest resemblance to HAND–SCHÜLLER–CHRISTIAN disease; in both diseases defects appear in a solid fibrous envelop of a part of the nervous system, in the latter in the bony skull surrounding the brain, in the former in the fibrous sclera surrounding the retina. In either disease the forming of the defect is preceded by the appearance of more or less soft subcutaneous or subconjunctival elevations, containing lipo-lipoid substance. The other symptoms differ; in scleromalacia the joints are involved, in HAND–SCHÜLLER–CHRISTIAN disease lipo-lipoid substance is deposited in the orbit and the base of the skull, but in either disease nearly all other organs may be affected eventually.

Whether in lipoidosis cholesterica xanthomatosis will express itself in the form of generalized xanthomatosis with many nodules in skin and subcutaneous tissue or in the form of HAND–SCHÜLLER–CHRISTIAN disease or as scleromalacia perforans will be mainly dependent upon a constitutional factor, viz. the degree of cholesterophilia of the various tissues, as in all these three cases the deviations from the norm in blood and tissue fluid will probably be equal. If the sclera is most ready to receive cholesterol, scleromalacia makes its appearance, if, on the other hand, skull and orbit get the better of the sclera in this respect, HAND–SCHÜLLER–CHRISTIAN disease appears, whereas xanthomatosis universalis may arise in case of great cholesterophilia of skin and subcutaneous tissue. The degree of cholesterophylia also accounts for the reason why these diseases, arising from the same cause, coincide so very rarely. In the syndrome of scleromalacia it depends upon the cholesterophilia of the joints whether or not they will be affected.

When introducing the factor of cholesterophilia (SIEMENS) or lipoidophilia POLANO), the nature of which is utterly unknown, we only transfer our difficulty it is true, but yet much becomes clearer in the province of lipoidosis cholesterica.

Prognosis: Prognosis of scleromalacia perforans is guarded. In spite of the uvea being exposed, a prolapse of the iris may continue to exist for many years, but, at any moment, infection may destroy the eyes, articular affections may impede mobility, cardiac and renal affections may threaten life.

Therapy: As a radical therapy we may try to influence the process favourably by withholding all steroids from the food, but we know that this need not be effectual, because the organism may build up cholesterol out of sources that are unknown to us. As a palliative therapy we must cover all scleral defects with firm mucous membrane in order to prevent infection.

Though being convinced that a number of our cases of scleromalacia

perforans, (as all patients examined for it), falls into the class of lipoidosis cholesterica, yet far be it from me to assert that all cases of scleromalacia are caused by such a lipoidosis cholesterica. Probably several causes may bring about the same manifestations, as is usually the case. The defects, observed by KUHNT [27]) in that part of the sclera which is exposed in the slit of the eye in a patient affected with hydroa vacciniforme, and which are to be compared with the defects in scleromalacia perforans, are presumably caused by a chemical agent, that makes its appearance in these patients under the influence of irradiation.

It is almost certain that, apart from these, other causes are underlying scleromalacia perforans. Prof. G. F. ROCHAT informed me, that although they had been closely examined, no disturbances of cholesterol metabolism could be found in some of his patients, affected with scleromalacia perforans.

Nevertheless this proof is not conclusive, for in our case V, attended by so severe a dyslipoidosis cholesterica, no sign of the disturbance of cholesterol metabolism was to be found in the serum and moreover one should take into account that there is a possibility of this disturbance having existed previously and having given rise to the defects, but now no longer being present.

In spite of these difficulties we have to assume, at the present state of our knowledge of this problem, that lipoidosis cholesterica is but one of the causes of scleromalacia perforans.

Scleral affections are relatively rare; in these rare affections the combination of articular diseases and scleral affections is relatively frequent.

Rheumatism is a cause of both of them, and in lues and tuberculosis both scleral and articular affections may occur. There seems to be a great resemblance between sclera and joints as regards susceptibility to the same diseases.

A very interesting affection, by which both sclera and joints may be affected and which may be compared with scleromalacia perforans in many respects, is ochronosis.

In 1866 VIRCHOW [28]) designated as such, a condition, marked by green and black pigmentation of many parts of the body. BOEDEKER [29]) (1859) had described before an affection, which he designated as alkaptonuria, in which the urine became darkbrown in colour, either directly after voiding, or when placed in the air or on addition of alkali. Afterwards alkaptonuria and ochronosis were found to be closely related, although ochronosis does not occur in every case of alkaptonuria nor alkaptonuria in every case of ochronosis.

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[27]) KUHNT l.c.

[28]) Virchow's Archiv 37, 212.

[29]) BOEDEKER, Zeitschrift f. rat. Mediz. 1859, 7, 130.

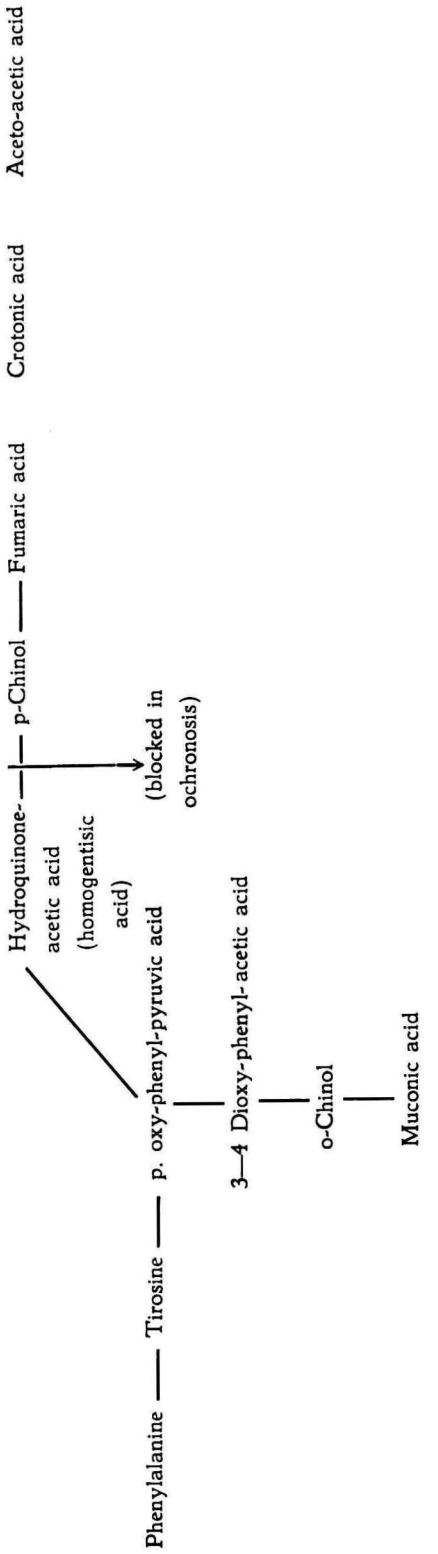
In ochronosis the most outstanding feature is the greenish colour of the nose, face and concha auriculae (Fig. XXVII), whilst the sclera, lying in the eye slit, may present a gray or brown colour.

At first this affection was thought to be of minor importance to the patient, and at most to entail complaints of cosmetic nature in view of the abnormal colour of the face, but soon it was found that this affection could have serious consequences on account of severe arthritis deformans besides slight articular affections.

The patient, shown in Fig. XXVII, suffering from ochronosis, could not leave his bed because of the articular affections, whilst his brother, who presented the same colour, had slight articular affections, causing pain and his cervical vertebrae made snapping sounds when in action.

A number of autopsies revealed that the pigment may be present in numerous organs, in all cartilages, in the intima of the arteries, in connective tissue, tendons, ligaments, dura mater, in endocardium and kidneys. The disease was found to be a congenital disorder of protein metabolism. In the diapers of the newborn brownish-black spots of alkaptonuria was observed. The affection is hereditary and familial, the inheritance is recessive, often father and mother of the patients are cousins.

In normal cases the splitting of proteins in the body takes place as follows:



In patients suffering from ochronosis the splitting of proteins ends at homogentisic acid stage; this remains in the body therefore and has a toxic action. This is a typical intoxication by a chemical agent, caused by a congenital disturbance of metabolism, an endogenous intoxication, but it is very interesting, that this very affection may be caused by an exogenous intoxication e.g. carbolic acid. Formerly ulcera cruris were often treated with carbolic acid dressings, and treatment was sometimes continued for years. Carbolic acid intoxication, on the base of these dressings, provoked the very picture ochronosis does in disordered metabolism. Articular affections are of more rare occurrence here, probably because they do not arise until the intoxication has been of much longer duration and the intoxication must be more intensive; numerous internal parts of the body obtain an intensive colour in carbolic acid poisoning.

Besides disordered metabolism and carbolic acid poisoning there are some unknown causes, that may give rise to ochronosis. R. HEYMAN [30]) found in thirty-three cases of ochronosis seventeen cases of alkaptonuria, eight cases, in which carbolic acid had been used for some years, whilst in eight cases the etiology remained obscure. The resemblance of ochronosis and scleromalacia perforans is very great, as we see here, they may both be diseases of the metabolism, the former of protein, the latter of cholesterol, both of them may originate in an intoxication, ochronosis by carbolic acid, which is an ascertained fact, scleromalacia perforans probably by an unknown chemical agent occurring in hydroa vacciforme, which is attended by porphyrinuria, in both of them some unknown causes are also playing a part.

Both of them affect sclera and joints and, in the long run, they may affect numerous other organs as well, such as heart, kidneys, vessels, bones etc.

The colour of the sclera may change on account of various causes: which are shown in outline on page 39.

Scleromalacia senilis (Fig. XXVIII) occurs often in elderly people, the sclera becomes thinner at the level of the insertion of the horizontal ocular muscles.

When now considering the conclusions we may draw from the data communicated, we find:

I.

Nomenclature, definition and classification of lipoids and fats are not satisfactory, it would be greatly advisable to subject them to a thorough revision.

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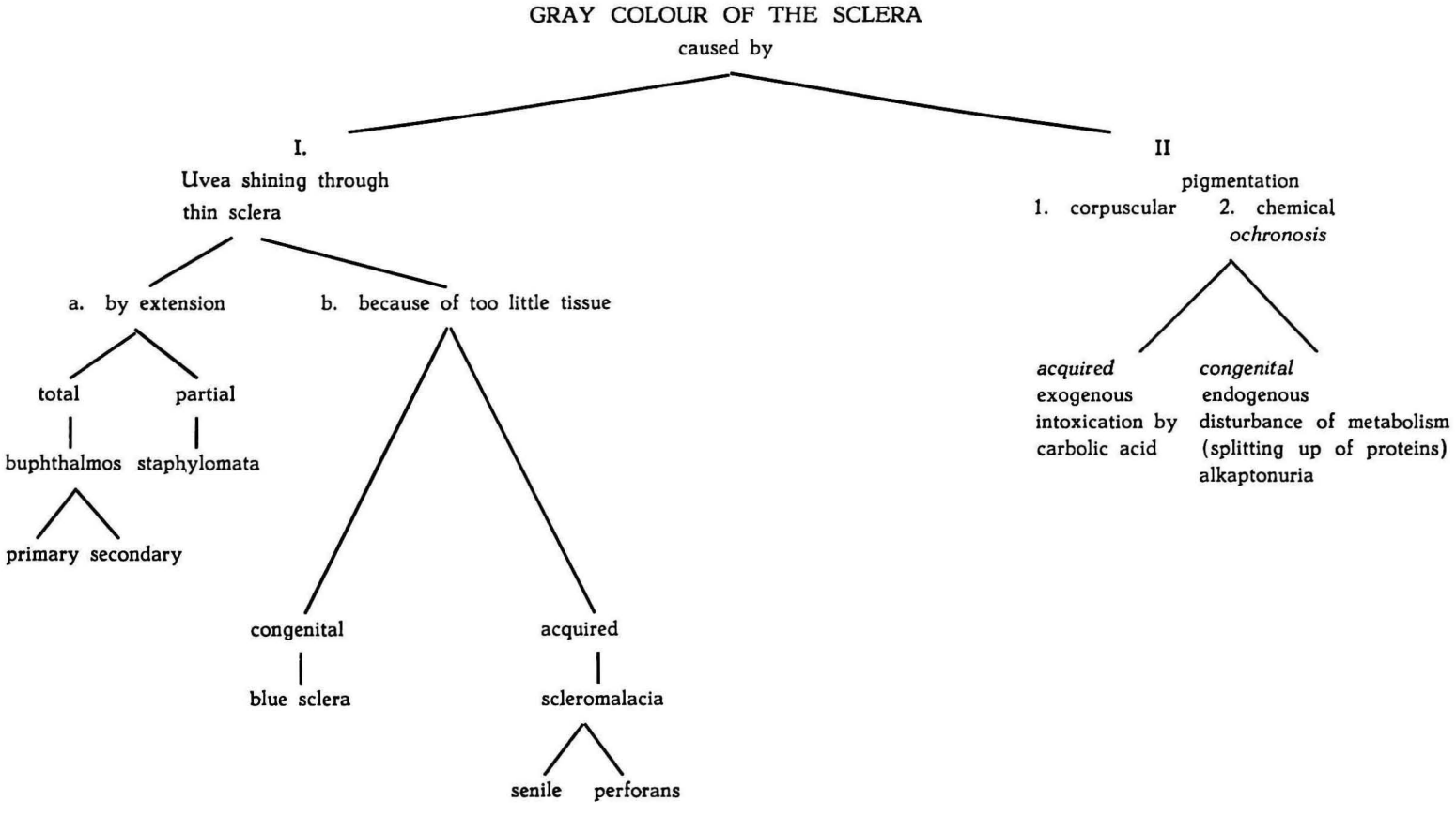
[30]) Quoted after LICHTWITZ: Alkaptonurie. Handbuch der inneren Medizin von BERGMANN and STAEHLIN, Vol. IV, part 1, p. 969.


GRAY COLOUR OF THE SCLERA
caused by
I.
Uvea shining through thin sclera
a. by extension
b. because of too little tissue
total
partial
buphthalmos
staphylomata
primary
secondary
congenital
blue sclera
acquired
scleromalacia
senile
perforans
II
pigmentation
1. corpuscular
2. chemical
ochronosis
acquired
exogenous
intoxication by carbolic acid
congenital
endogenous
disturbance of metabolism (splitting up of proteins)
alkaptonuria

II.

Lipoidosis cholesterica may be subdivided in hyperlipoidosis; hypolipoidosis and dyslipoidosis cholesterica, which diseases may occur separately or in combination.

III.

Scleromalacia perforans is a syndrome, principal symptoms of which are:
Degeneration of the sclera attended by the formation of defects.
Lipoidosis cholesterica.
Articular affections, even arthritis deformans, whilst as less frequent manifestations all symptoms of xanthomatosis may be present, which may finally affect nearly all organs.

IV.

Lipoidosis cholesterica may be the cause of all cardinal and accessory symptoms of scleromalacia perforans.

V.

Besides lipoidosis cholesterica there are also other causes of scleromalacia perforans; in the only case of scleral defects, recorded in literature, occurring in hydroa vacciniforme, the cause is probably a chemical intoxication by a substance formed under the influence of irradiation.

VI.

Lipoidosis cholesterica may exist and even exist to a considerable degree, without a change of the cholesterol proportions in the blood being demonstrable.

VII.

Lipoidosis cholesterica may give rise to xanthomatosis universalis, HAND–SCHÜLLER–CHRISTIAN disease, scleromalacia perforans and other affections.
In all probability it is dependent upon the degree of cholesterophilia of the various tissues, which disease will make its appearance.

VIII.

Scleromalacia perforans bears a close resemblance to ochronosis, either may result from disordered metabolism, probably from intoxications as well, whilst in either disease some unknown causes may also play a part. They affect both sclera and joints, and may even result in an arthritis deformans, both diseases may affect nearly all organs ultimately.

FIRST PICTURE.

Xeroderma pigmentosum.

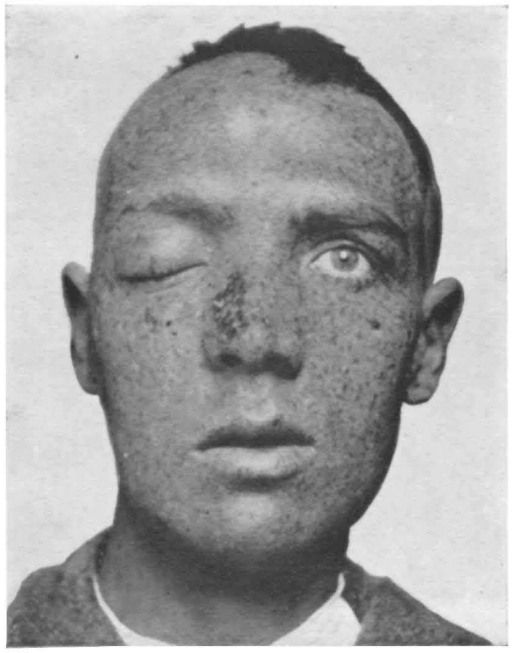
Fig. I. Epithelioma on the nose. Ptosis caused by a paralysis of the right oculomotor nerve.

Fig. II. Wide pupil of the right eye and outward deviation of the eye caused by a paralysis of the oculomotor nerve.

Fig. III. Metastasis of epithelioma in the substance of the brain.

Fig. IV. Metastases of epithelioma in the base of the skull in bone and pituitary body.

I.



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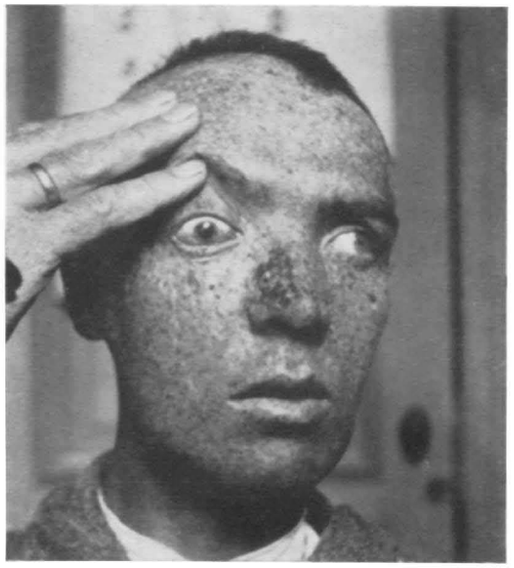

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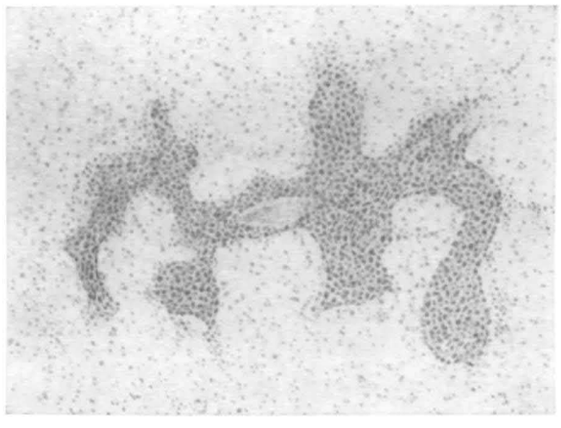
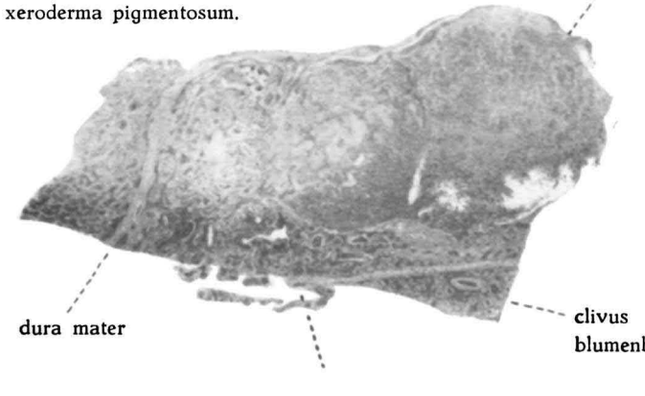


IV.

Metastatic epithelioma in the skull in xeroderma pigmentosum.



PICTURE II and III.

Cholesterol crystals in cornea.

Fig. V. Centre of cornea still free. Visual acuity following correction 9—10/10.

Fig. VI. Cholesterol crystals in the cornea, pupil completely covered.

Fig. VII—XIV *Cholesterol granulation mass in cornea.*

Fig. VII. August 1921. Pupil partly free. Visual acuity following correction 4—5/10.

Fig. VIII. June. 1923. Small part of the cornea still free. V = 1/60.

Fig. IX. March 1924. Cornea entirely vanished into the mass. Eye blind.

Fig. X. August 1921. One xanthoma-focus in the cornea. V = 8—9/10.

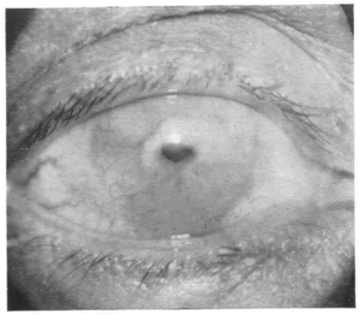
Fig. XI. November 14, 1923, first focus has spread, new focus independent of the first one. V = 8—9/10.

Fig. XII. March 1924, the two foci have extended and become one, small part of the pupil is still free. V = 6/10.

Fig. XIII. September 1924. New little focus, just before the small surface of the pupil. V = 1/10.

Fig. XIV. Xanthoma in chamber with many gaps, in which cholesterol crystals were lying.

V.



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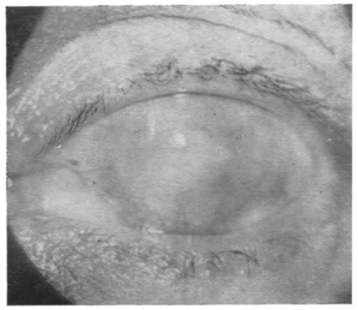

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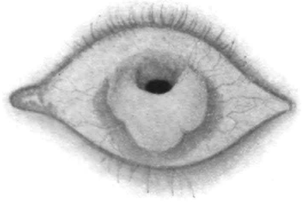

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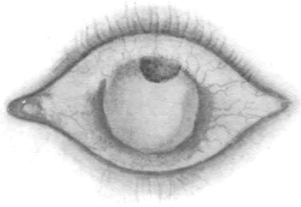

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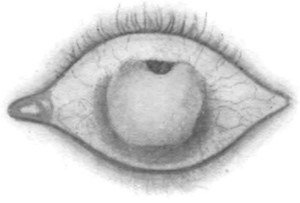

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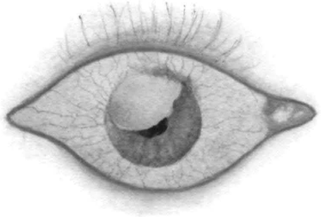

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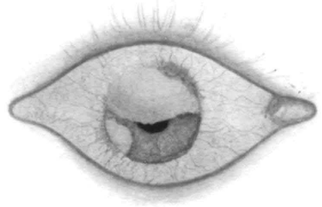

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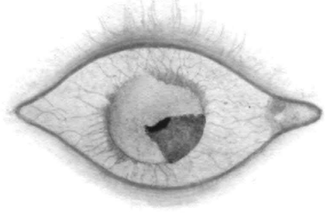

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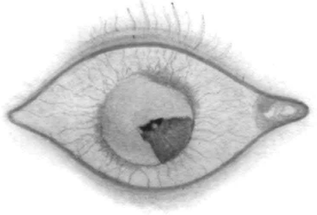

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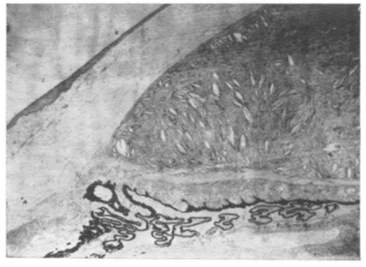


PICTURE IV.

Scleromalacia perforans.

Fig. XV. Cornea opaque with crystals, large number of gaps in the sclera, some of them have become confluent.

Fig. XVI. Great arcus senilis, small vertical slit in the sclera near the limbus and formation of cyst.

Fig. XVII. Deposit of cholesterol crystals in cornea, small defect in the intercalary part of the sclera, large prolapse of the iris.

Fig. XVIII. Little hole in sclera, large prolapse of the iris.

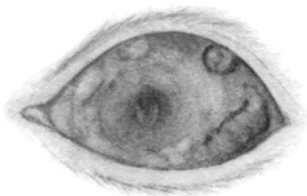
Fig. XIX. Small non-perforating gap at the inner aspect of the sclera, symmetrical with the gap in the other eye (Fig. XVIII).

PICTURE V.

Fig. XX. Scleromalacia perforans posterior? In the area of the macula a white mass (cholesterol crystals?), which force their way through the yellow macula.

Fig. XXI. Scleromalacia perforans. Eye ball presenting two large defects in the sclera, separated by a narrow strip of sclera.

XV.



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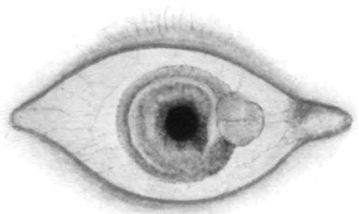

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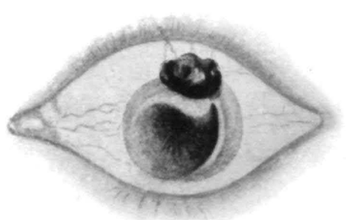

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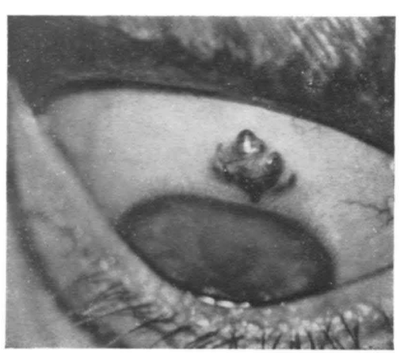

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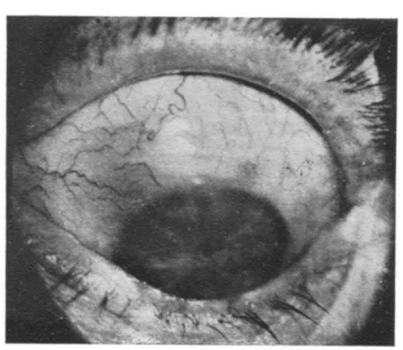

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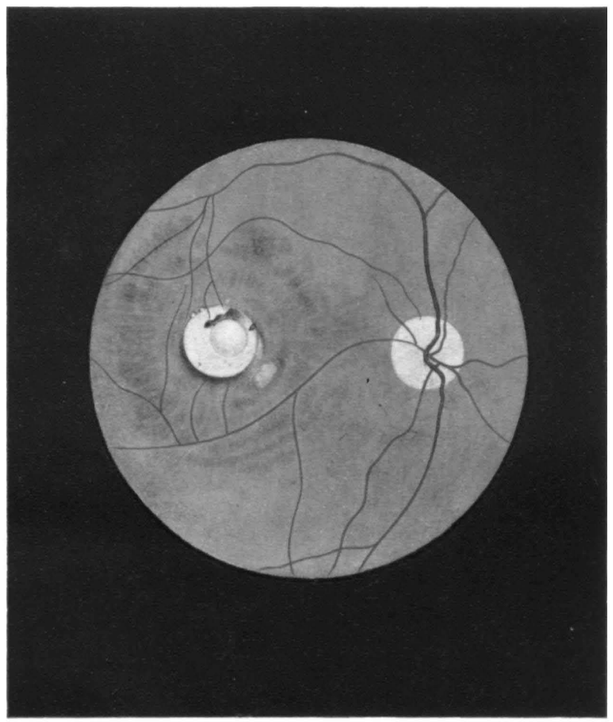

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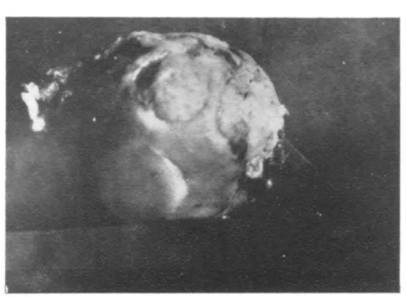


PICTURE VI and VII.

Scleromalacia perforans.

Fig. XXII and XXIII. Initial stage in 1938, with yellow and gray lobate masses in the episclera.

Fig. XXIV. Terminal stage in the same patient in 1940; enermously large gap from limbus corneae to far behind the equator, in which ciliary body and chorioid are exposed, the borders of the gap seem to be gnawed at.

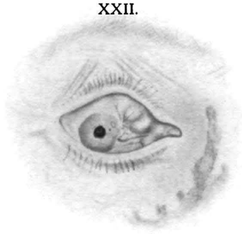
Fig. XXV. Microscopic slide of the same eye. Large defect in the sclera extending from the limbus corneae, lipoid granulation masses in ciliary body, choroid and sclera. Scleral fibrils like a sequester in granulation mass.

Fig. XXVI. Detail of Fig. XXV.

Fig. XXVII. *Ochronosis.* Gray-green colour of ear and nose, gray brown colour of the sclera in the eye slit.

Fig. XXVIII. Scleromalacia senile.

XXII.



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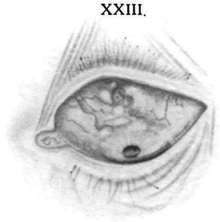

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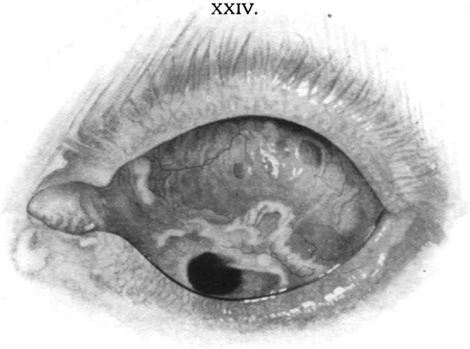

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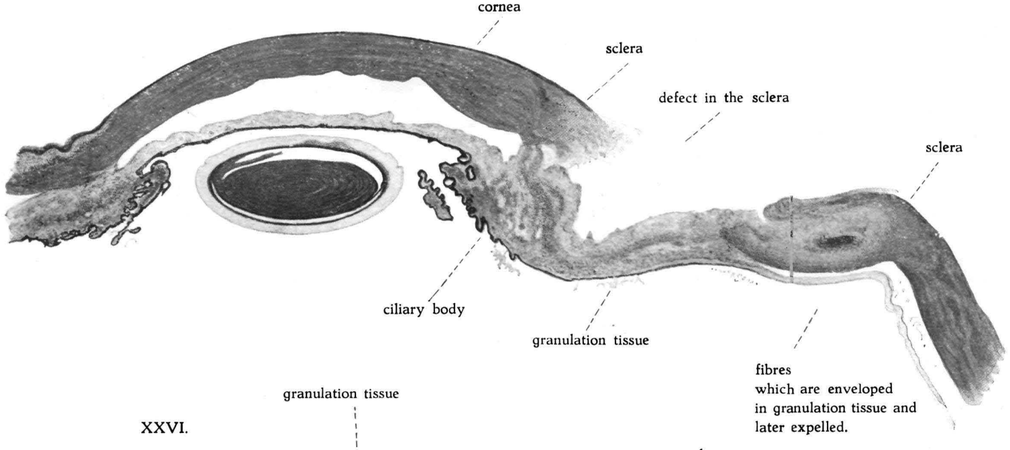

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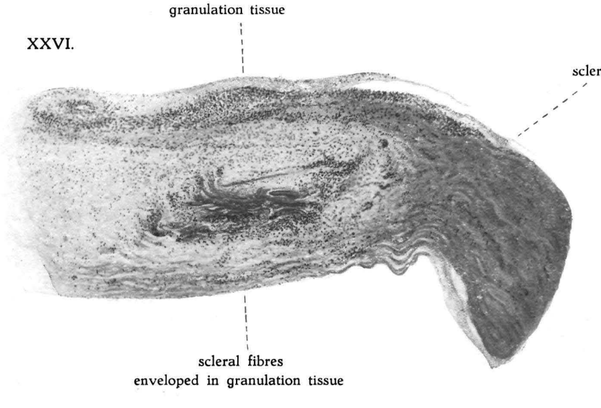

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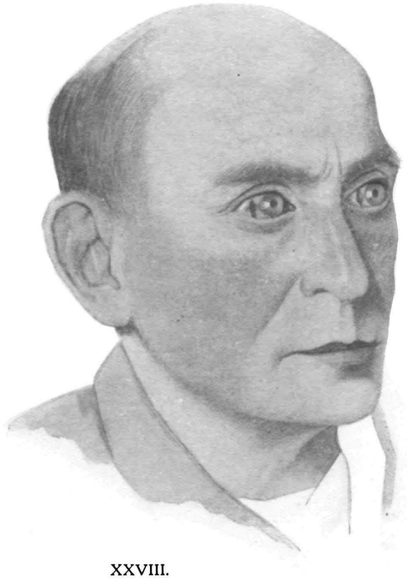

XXVIII.