TAPETORETINAL DEGENERATIONS AND DISORDERS OF LIPID METABOLISM

Part II: Biochemical Aspects

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Inherited tapetoretinal degenerations associated with, or caused by, abnormalities in lipid metabolism are discussed in terms of recent findings regarding their etiology. The biochemical basis of these tapetoretinal degenerations may be summarized as follows.
(a) *In abetalipoproteinemia (the Bassen-Kornzweig syndrome) there is a complete absence of all plasma lipoproteins except HDL (alfalipoprotein; high density lipoprotein). In addition the levels of plasma lipids, including vitamin A, are grossly dimished. The genetically-caused basic defect in this disorder is the absence of a specific protein component, apoLP-ser, in the plasma lipoproteins.*
(b) *In a milder form of hypobetalipoproteinemia, transmitted as an autosomal dominant trait, there is little, if any, retinal degeneration.*
(c) *Refsum's syndrome is characterized by greatly increased plasma levels of phytanic acid, a 20-carbon branched-chain fatty acid. This substance is not synthesized in the body, but originates from dietary sources only. Patients with Refsum's syndrome lack the enzyme (phytanic acid oxidase) necessary to oxidize this fatty acid, and its accumulation in the tissues has severe consequences. Therapeutic measures, consisting of restriction of dietary phytanic acid, have given encouraging results.*
(d) *Three forms of Batten's disease (neuronal ceroid lipofuscinosis) are now recognized. These are* (1) *the rapidly progressive (Jansky-Bielschowsky) form,* (2) *the chronic (Batten-Mayou-Vogt-Spielmeyer-Sjögren) form, which is the most common, and* (3) *the late onset (Kufs') form. All are associated — to varying degrees — with an accumulation of autofluorescent ceroid-lipofuscin pigments. The enzymatic defect is believed to consist of abnormalities in peroxidase enzymes.*
(e) *Other tapetoretinal degenerations thought to be associated with defects in lipid metabolism are discussed briefly. These include Hooft's disease, Cockayne's syndrome, and Alstrom's syndrome.*

To the clinician, the principal emphasis in genetic disorders is in diagnosis, counseling, and treatment, when this is possible. But to biochemists and other research investigators, these rare errors of nature provide valuable information not only about normal cellular metabolism, but also in many instances serve as the stimulus for uncovering metabolic sequences that had previously eluded investigators. A recent example of this is the intracellular degradation of mucopolysaccharides. The breakthrough in this field has come from the exciting investigations of Dr. Neufeld and her coworkers at the National Institutes of Health (Neufeld 1972,

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TABLE 1

LEVELS OF SOPHISTICATION LEADING TO AN UNDERSTANDING OF INBORN ERRORS OF METABOLISM
[*Adapted from Raivio and Seegmiller 1972*]

1	*Description of phenotype*	Clinical presentation, natural history, pathological features, etc.
2	*Proof of genetic origin*	Establishing mode of genetic transmission
3	*Delineation of biochemical abnormality*	Characterization of abnormal metabolites
4	*Elucidation of basic defect*	Enzymatic deficiency, structural abnormality, etc.
5	*Identification of the primary mutational event*	Elucidation of the abnormal chromosomal DNA sequence (or abnormal substitution or deletion)

Bach et al., 1973), and, as a result, techniques are now available not only for classifying the various mucopolysaccharidoses, but also for determining the enzymatic defects. Unfortunately we have not as yet reached this stage for the lipidoses.

A true understanding of any inborn error of metabolism proceeds through five levels of sophistication, as shown in Table 1. It is especially the information in the last three stages that leads to rational forms of therapy, the principal ones in use today being enzyme replacement and dietary restrictions.

Most of the tapetoretinal degenerations known to us at the present time, that are caused by, or associated with, abnormalities in lipid metabolism, are summarized in Table 2. Other disorders, in which lipid involvement is suspected, but its exact nature not yet clearly established, will be discussed later. The heterogeneity of the biochemical defects in this group of diseases is obvious, and one wonders what type of unifying concept can be offered to explain the specific ocular changes in these syndromes. Although our knowledge is far from complete, there are nevertheless several examples where the tapetoretinal degeneration can be explained in terms of either the basic biochemistry of the pigment epithelium or of an essential role of

TABLE 2

TAPETORETINAL DEGENERATIONS RESULTING FROM ABNORMALITIES IN LIPID METABOLISM

	Name of disorder	Biochemical defect
I	Plasma betalipoprotein deficiencies	
	A. Abetalipoproteinemia (Bassen-Kornzweig syndrome)	Absence of apoLP-ser in plasma lipoproteins
	[B. Hypobetalipoproteinemia*	Low LDL]
II	Refsum's syndrome	Absence of phytanic acid oxidase
III	Batten's disease or neuronal ceroid lipofuscinosis (NCL)	Accumulation of ceroid lipofuscin
	A. Jansky-Bielschowsky (rapidly progressive form)	
	B. Batten-Mayou-Vogt-Spielmeyer-Sjögren (chronic form)	
	C. Kufs' (late onset form)	

* This disorder should probably not be included since eye changes are doubtful.

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these cells in the normal functioning of the photoreceptors. This information has led to the development of specific diagnostic tests for the detection of some of these disorders (Warburg 1972, Berman 1973).

1. PLASMA BETALIPOPROTEIN DEFICIENCIES

1.1. *Abetalipoproteinemia*

This disorder was first known as the Bassen-Kornzweig syndrome (Bassen and Kornzweig 1950, Kornzweig and Bassen 1957), and later as acanthocytosis, because of the peculiar and characteristic morphology of the red blood cells. The discovery of a complete absence of plasma betalipoproteins necessitated revising the name to the presently used biochemical term (Salt et al. 1960).

Abetalipoproteinemia is transmitted as an autosomal recessive trait and, although a large proportion of the affected families are of Jewish or Italian origin, nevertheless it has also appeared in other groups such as French and Scottish (Fredrickson et al. 1972). As we shall see, the disorder cannot be detected in heterozygotes because the basic enzymatic defect is still not known, i.e., we have only reached stage 3 in our level of understanding of this syndrome (Table 1).

1.1.1. *Chemical Pathology*

Of all the biochemical abnormalities present in this disorder, the most striking is the complete absence of plasma betalipoproteins (Fig. 1) concomitant with grossly diminished levels

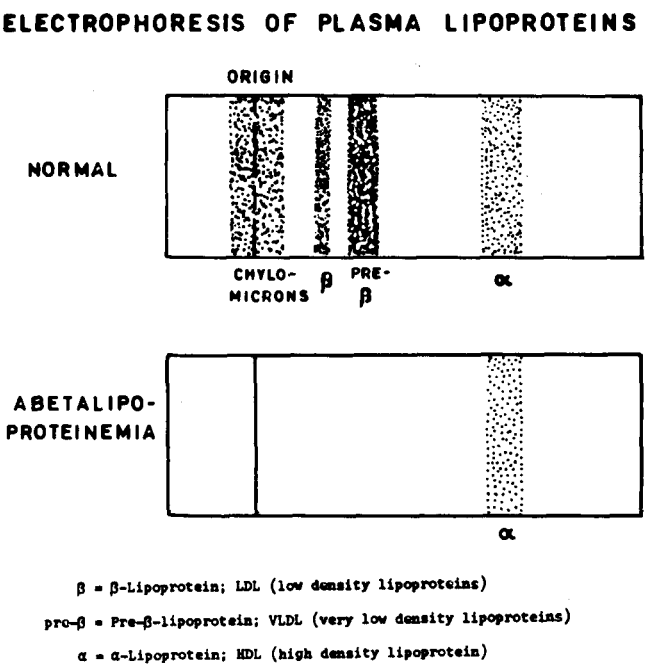

Fig. 1. Schematic representation of plasma lipoproteins after paper electrophoresis.
The upper electropherogram is that of a normal individual, and the lower one, that of a patients with abetalipoproteinemia.

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of plasma lipids (Table 3). The main types of lipoproteins normally present in the circulating plasma (Fig. 1) are chylomicrons, betalipoproteins (LDL, low density lipoproteins), prebetalipoproteins (VLDL, very low density lipoproteins), and alfalipoproteins (HDL, high density lipoproteins). The only plasma lipoprotein detectable in patients with abetalipoproteinemia is one whose electrophoretic mobility is the same as that of normal alfalipoprotein. It is however an abnormal type of alfalipoprotein both in its immunological properties and in its behavior in the ultracentrifuge, where it flotates at a density similar to that of LDL. The diminished plasma levels of lipids in these patients (Table 3) are the result of the betalipoprotein abnormalities.

Recent studies suggest that the basic defect in abetalipoproteinemia lies in the composition and/or structure of the protein components, the apoproteins, of the plasma betalipoproteins. The chemistry of these substances is an extremely complex subject, and further details may be found in several excellent recent reviews (Fredrickson et al. 1972, Kayden 1972). Suffice it to say that in patients with abetalipoproteinemia, a specific protein called apoLP-ser[1] is absent. This substance is the major protein component of chylomicrons as well as of LDL and VLDL (Gotto et al. 1971).

TABLE 3

COMPARISON OF PLASMA LIPID LEVELS IN NORMAL INDIVIDUALS AND IN ABETALIPOPROTEINEMIA
[*Adapted from Fredrickson et al. 1972*]

	Age	Cholesterol (mg/100 ml)	Triglycerides (mg/100 ml)
Normal	1-19	120-130	10-140
Abetalipoproteinemia	7-37	35-72	1-10

1.1.2. *Pathogenesis of Ocular Lesion and Therapy*

What are the consequences of the absence of this specific protein, apart from the severe hypolipidemia so characteristic of this disorder? The principal one, of greatest interest to the ophthalmologist, is the almost complete absence of vitamin A and carotenoids in the circulating plasma. The reason for this is still obscure since, although low vitamin A levels are often ascribed to the generalized malabsorption of fats in individuals with abetalipoproteinemia, this is not the whole explanation. Normally, vitamin A is not absorbed in the free form, but is first esterified with palmitic acid (Fig. 2). This ester circulates initially with the chylomicrons and later with the low-density lipoproteins *before* being stored in the liver (Kayden 1972). When vitamin A is released from the liver for transport to various tissues, it is as the free alcohol bound to a specific low-molecular-weight protein called RBP (retinolbinding protein). This vitamin A-RBP complex, in turn, forms another complex with pre-albumin, which functions as the main carrier in the plasma. The vitamin A is believed to enter the tis-

[1] An apoprotein component of serum lipoproteins having serine as the carboxyl terminal aminoacid.

sues together with the RBP, to which it is tightly bound, while the pre-albumin remains in the circulation.

It is generally assumed that the retinitis pigmentosa which develops in abetalipoproteinemia is the direct consequence of the vitamin A deficiency. If this is so, then administration of vitamin A to these patients should reverse — to a greater or lesser extent — the abnormalities both in visual threshold and in ERG responses. Negative results were reported a decade ago in the first clinical trial with vitamin A (Wolff et al. 1964) but, more recently, other clinical trials have produced more encouraging results (Gouras et al. 1971, Sperling et al. 1972). The prognosis is more encouraging the earlier the vitamin A therapy is undertaken, i.e., before permanent and irreversible retinal damage has taken place.

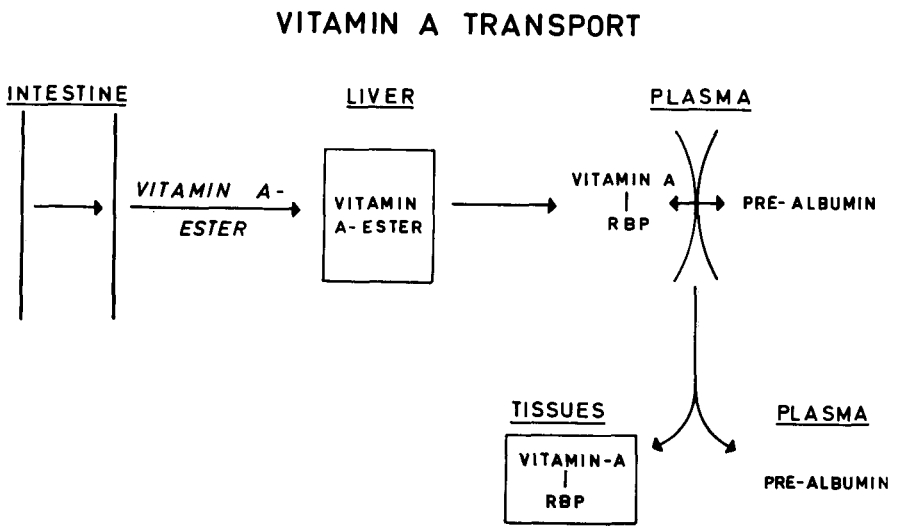

Fig. 2. Simplified sketch of vitamin A metabolism showing transport from the intestine to the liver, storage as esterified vitamin A, and release and transport in the blood as an RBP-vitamin A complex carried with the pre-albumin fraction of the blood.

Nevertheless, we are still not certain whether vitamin A deficiency alone is the *only* factor responsible for the retinitis pigmentosa. In order to establish this with more certainty, patients would have to be treated at the earliest possible age with amounts of vitamin A sufficient to maintain normal serum levels. If this prevented the onset of the retinitis pigmentosa, it would provide sound evidence implicating vitamin A. It should however be pointed out that pigmentary retinopathy of this type has never been described in vitamin A deficiency states in either man or animals, although night blindness and ERG changes are well documented.

Moreover, in human retinitis pigmentosa, despite an early report of decreased plasma vitamin A levels (Campbell et al. 1964), it appears that in most patients with this disorder, the serum vitamin A levels are in fact within normal limits.

If not vitamin A " deficiency " alone, what then is the etiology of the tapetoretinal degeneration in abetalipoproteinemia? I would like to postulate (without direct experimental evidence) that the same abnormality causing the acanthocytosis of the erythrocytes plays

a role in the pathogenesis of the pigment-cell degeneration. Unfortunately, we do not understand the biophysical factors leading to the formation of the thorny projections present in 50% or more of the erythrocytes in these patients. It has been suggested (Fredrickson et al. 1972) that acanthocyte formation could be a consequence of either (*a*) a defect in the phospholipid structure of the erythrocyte membrane, (*b*) an abnormal response by the red cell membrane to a plasma milieu deficient in betalipoproteins, or (*c*) a lack of some essential component transported by the betalipoproteins. Von Sallmann et al. (1969) described the shoddy mottled appearance of the pigment epithelium, and I am tempted to speculate that the initial lesion is caused by either an abnormality in the phospholipid components of the pigment epithelial cells or in an inability of these cells to maintain their normal shape and structure due to disturbances in the microenvironment. We have recently examined the phospholipids of pigment epithelial cells as a first step in long-range studies on these cells, and found them to contain only lecithin. Other phospholipids are completely absent. These investigations were carried out on bovine pigment epithelial cells and, hopefully, analogous studies on normal human tissue and in abetalipoproteinemia patients, will shed further light on the etiology of the tapetoretinal degeneration.

1.2. *Hypobetalipoproteinemia*

As indicated in Table 2, there is some question of whether this disorder should be included as a tapetoretinal degeneration. These patients are usually asymptomatic clinically, and most of them have been found through presenting signs unrelated to this disorder. Although first reports suggested the presence of mild retinal pigmentation (van Buchem et al. 1966), others have found no such changes (Mars et al. 1969).

Hence this autosomal dominant " forme fruste " of abetalipoproteinemia, of which four kindred are presently known (Fredrickson et al. 1972) should not at the moment be considered among the tapetoretinal degenerations.

2. REFSUM'S SYNDROME

Five cases of this rare neurological syndrome were originally reported by Refsum in two inbred Norwegian families (Refsum 1946); since that time about 45 additional cases have been reported; we know of three more (in a single family) in Israel. The disorder is transmitted as an autosomal recessive trait and at the present time we have reached stage 4 in our level of understanding of this inborn error of metabolism (Table 1).

2.1. *Chemical Pathology*

Greatly increased plasma levels of phytanic acid are the hallmark of Refsum's syndrome (Steinberg 1972). This 20-carbon branched-chain fatty acid is also deposited in the visceral tissues, especially liver and kidney. Phytanic acid is not synthesized in the body (Fig. 3); it originates mainly from dietary sources, e.g., animal fats. Secondarily, it also derives from phytol, a component of leafy vegetables.

The metabolic defect in this syndrome is the absence of phytanic acid oxidase (Fig. 3), an enzyme that oxidizes phytanic acid by one-carbon degradation. This is in contrast to the usual mechanism of fatty acid oxidation which, in nearly all mammalian tissues, is by two-

carbon degradation. One-carbon oxidation has so far been demonstrated only in brain and nervous tissue, where this metabolic pathway apparently plays an important, though little understood, role.

In patients with Refsum's syndrome, the inability to oxidize phytanic acid has been demonstrated both *in vivo*, after administration of labeled phytanic acid (Steinberg 1972), and in cultured skin fibroblasts (Herndon et al. 1969).

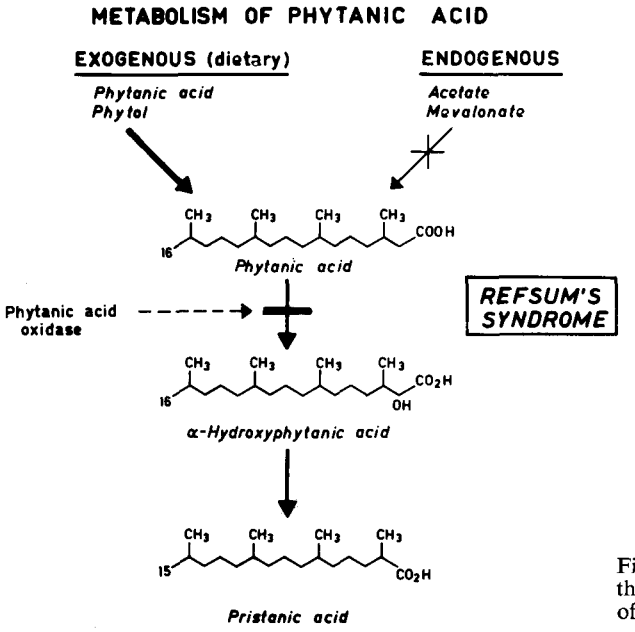

Fig. 3. Metabolism of phytanic acid, showing the block in Refsum's syndrome at the step of phytanic acid oxidase.

2.2. *Pathogenesis of Ocular Lesion and Therapy*

In the only ocular pathologic study reported to date (Toussaint and Danis 1971), heavy sudanophilic substances — undoubtedly lipid in nature — were present in sclera and trabecular tissues as well as in the pigment epithelium of the posterior, equatorial, and peripheral fundus. The rods and cones were almost entirely missing, and the outer nuclear and outer plexiform layers appeared grossly atrophic. Other abnormalities were also found.

Although there is no direct proof, it is reasonable to assume that the pathological changes observed are the consequence of a massive infiltration of phytanic acid into the pigment epithelium. It has been suggested that the accumulation of this substance in the interphotoreceptor space interferes with the transfer of essential nutrients, as well as intermediates of the visual cycle, between the outer segments and the pigment epithelial cells. Once this metabolic interchange is disturbed, subsequent degenerative changes in the photoreceptors would be expected.

This brings us then to the question of reversibility. To what extent can the extensive damage done to the retina after years of infiltration of phytanic acid be reversed? Steinberg

and his associates (Steinberg et al. 1970) showed that in patients with Refsum's syndrome, definite clinical improvement resulted after instituting a low phytol-low phytanic acid diet. Concomitant with a striking fall in serum phytanic acid levels, there was a marked improvement in muscle strength, dexterity, and motor nerve conduction velocities. The visual acuity of one of the patients also improved considerably [2] (Kark et al. 1971).

These findings suggest that the ocular lesion is indeed a consequence of the accumulation of phytanic acid, either within the pigment epithelial cells, or on the surfaces of these cells. Apparently if the ocular damage has not proceeded to an irreversible stage, then withdrawal of phytanic acid from the diet results in a slow release of this lipid from the tissues where it has accumulated. It is this withdrawal from bound sites that probably leads to the partial restoration of visual acuity.

3. BATTEN'S DISEASE (NEURONAL CEROID-LIPOFUSCINOSIS: NCL)

For the past half century the term amaurotic familial idiocy has been used to describe a group of slowly progressive, hereditary neurological disorders that were differentiated from one another mainly on the basis of age of onset. This terminology, in the light of our present knowledge, is both confusing and erroneous since specific biochemical, enzymatic, or morphological defects now serve to define many of the disorders in this heterogeneous group.

TABLE 4

PROPOSED CLASSIFICATION OF SOME LIPID STORAGE DISEASE

Old names	Preferred new names	
	Gangliosidoses	Lipidoses
Infantile amaurotic idiocy (Tay-Sachs disease)	G_{M2}-Type I	
Sandhoff's disease	G_{M2}-Type II	
Juvenile G_{M2}-gangliosidosis	G_{M2}-Type III	
Familial neurovisceral lipidosis (Generalized gangliosidosis)	G_{M1}-Type I	
Late infantile systemic lipidosis (Derry 1968)	G_{M1}-Type II	
Late infantile amaurotic idiocy (Jansky-Bielschowsky)		Batten's disease or neuronal ceroid lipofuscinosis (NCL) (Zeman 1970 and Kolodny 1972)
Juvenile amaurotic idiocy (Batten-Vogt-Spielmeyer)		
Adult amaurotic idiocy (Kufs' disease)		

In keeping with recent proposals to abandon the term amaurotic familial idiocy (Rouser and Wade 1969, Zeman and Dyken 1969, Zeman 1970 and 1971*a*, Gordon et al. 1972) new classifications based on biochemical nomenclature — when applicable — have recently been suggested (Zeman 1971*a*, Berman 1973). As shown in Table 4, one broad group includes

[2] From unable to count fingers at three feet on admission, to 20/400 after 9 months of dietary restriction, and 20/100 after 18 months.

the gangliosidoses, of which five types are presently known (O'Brien et al. 1971). The other group, in which ganglioside metabolism is normal (Zeman 1971*b*), has clinical signs that often overlap with those present in the gangliosidosis, and in the past led to the confusing terminology used in this field.

It is the second group of disorders that will — for the moment — be considered under the general name of Batten's disease. Zeman (1971*a*) believes that three clinical types can now be distinguished, all of them showing intracellular accumulation of ceroid-lipofuscin pigments, albeit to varying degrees.

A. The Jansky-Bielschowsky form (previously termed «late infantile form») is the most severe clinically. Its onset is between the ages of 1 and 4 years and it is characterized by generalized seizures and coma, leading to early death. Ocular signs consist of optic atrophy and granular macular degeneration; pigmentary changes are not prominent (Kolodny 1972).

B. The Spielmeyer-Sjögren or Batten-Vogt-Mayou form constitutes the majority of cases of neuronal ceroid lipofuscinosis (Kolodny 1972) of which over 175 have been reported throughout the world. It is this type that appears to be especially prominent among Scandinavian people (Sjögren 1931, Rayner 1962, and Warburg, personal communication). The onset is usually between ages 4 and 9, but may be as early as 2 years. Loss of central visual acuity and advanced retinal pigmentary degeneration are usually the first signs. Afterward there is progressive neurological deterioration until death, the average duration of the disease being about 11 years (Zeman 1971*a*).

C. The adult form, Kufs' disease, is extremely rare and does not seem to be accompanied by either seizures or visual disturbances; its course is very prolonged.

3.1. *Chemical Pathology*

The three types of Batten's disease described above have, as their common denominator, an accumulation of autofluorescent ceroid-lipofuscin particles in neurons, in leukocytic neutrophils, and in other tissues. The accumulation of these "storage substances" is considered to be the principal expression of the basic biochemical abnormality (Zeman and Dyken 1969, Zeman 1970, and Zeman et al. 1970). The visual disturbances characteristic of Batten's disease also may be the consequence of excess ceroid-lipofuscin within the pigment epithelial cells.

What is lipofuscin and what is ceroid? These terms have been used by pathologists and histologists for many years to designate autofluorescent pigmented bodies present in liver, heart muscle, neurons, and other tissues, that are presumed to be lipid in nature. Because of their absence in newborns and their gradual accumulation throughout lifetime, they have been collectively termed "age pigments". Very recently, the chemical nature of these substances has been greatly clarified through the investigations of Porta and Hartcroft (1969) and Siakotos and coworkers (Siakotos et al. 1970, Siakotos et al. 1972). Some of their findings are summarized in Table 5. It is now generally accepted that lipofuscin is a normal cellular component, representing breakdown products of lipid metabolism that accumulate slowly *inside* the cell. They are not extruded and may eventually be recognized as residual bodies. In contrast to this, ceroid is not a normal cellular component; it appears only in disease states, the most important one in the present context being Batten's disease.

Both ceroid and lipofuscin are extremely difficult to define morphologically because nei-

TABLE 5

COMPARISON OF SOME BIOCHEMICAL PROPERTIES OF LIPOFUSCIN ("AGE PIGMENT") AND CEROID

Properties	Lipofuscin	Ceroid
Present in healthy individuals	+*	—
Present in disease states**	+	+
Morphology (EM)	Cannot be distinguished from one another with certainty because of heterogeneity in size, shape, and degree of granulation	
Lysosomal acid hydrolases	+	+
Fluorescence spectra	Excitation 360 mm Emission 450 mm	Excitation 350 mm Emission 435 mm
Mass (density)	1.00-1.03	1.25-1.30
Cation composition	Zinc	Iron and calcium
Response to chelating agents	Insoluble	Soluble
Lipid composition	High concentration of "neutral" lipid polymers	High concentration of "acidic" lipid polymers thought to consist mainly of polyunsaturated fatty acids

* Approximately 0.01-0.02% of wet weight of normal human brain.
** E.g., induced choline or vitamin E deficiencies, various forms of liver cirrhosis, and Batten's disease.

ther has any unique distinguishing characteristics (Table 5). Both kinds of pigment particles are rich in acid hydrolases, suggesting a common lysosomal origin. Their fluorescence spectra are too close to distinguish one from the other when present together. Nevertheless, four important chemical properties may in fact be used to differentiate between the two. Ceroid is a heavier, i.e., more dense, particle than lipofuscin. In terms of cation composition, lipofuscin is rich in zinc while ceroid contains mainly iron and copper. This is believed to account for their different behavior toward chelating agents.

Finally, and most importantly, some progress has been made in determining the lipids composition of these pigments, and it is now generally believed that an "acidic" lipid, thought to consist of polymerized polyunsaturated fatty acids, is the major abnormal storage substance in Batten's disease (Siakotos et al. 1972). The "acidic" polymerized lipids accumulate in young individuals with Batten's disease in far greater amounts than they do during the whole lifetime of normal individuals. This phenomenon can be explained in two ways:

(*a*) Lack of enzymes that normally catalyze the breakdown of autofluorescent pigments to physiologically normal end products (e.g., residual bodies).

(*b*) Excess production of unsaturated fatty acids at a rate too rapid to be handled by the normal enzymatic machinery of the cell.

TABLE 6

FACTORS INFLUENCING PIGMENT FORMATION

Promote	Impede
Polyunsaturated fatty acids	Saturated fatty acids
+	+
Oxidative catalysts (e.g., hemes, free radicals, bivalent cations such as Cu^{++} and Fe^{++})	Antioxidants

With respect to this hypothesis (i.e., excess production) it is known that the rate of pigment formation is strongly influenced by two opposing sets of factors (Table 6). It seems that we are dealing with four variables, an abnormality in *any* of which could alter this delicate balance and result in uncontrolled pigment formation.

In support of this hypothesis, Hagberg et al. (1968) detected striking abnormalities in the concentration and distribution of certain polyunsaturated fatty acids in brain tissue of a child with Batten's disease. He postulated that these abnormal fatty acids could act as pigment precursors, undergoing peroxidation in the presence of divalent cations. This possibility has recently been put to a direct test by Menkes et al. (1972). Using both brain explants and skin fibroblast cultures from three patients with Batten's disease, evidence was provided suggesting faulty metabolism of linoleic acid, as shown in Fig. 4. Thus, linoleic acid is metabolized to unsaturated fatty acids containing 22 carbon atoms in Batten's tissues, in contrast to fatty acids containing 20 carbon atoms in normal tissues. Preliminary evidence suggests that the enzymatic defect is a specific peroxidase, one that uses p-phenylene diamine as acceptor (W. Zeman, personal communication). Whether this enzyme is also active on long-chain fatty acids remains to be established.

3.2. *Pathogenesis of Ocular Lesion and Therapy*

This aspect must remain highly speculative until we learn more of the biochemistry of the pigment epithelium, specifically some details about its lipid composition and metabolism. We know from the work of Feeney, Hogan, and others (Feeney et al. 1965, Hogan et al. 1971) that lipofuscin granules accumulate in the pigment epithelium of most — or possibly all — elderly individuals. Although this has not been investigated directly in Batten's disease, it is reasonable to assume that lipofuscin and/or ceroid accumulate in these cells as well. The presence of these abnormal storage substances accumulating at a very rapid rate could lead to visual disturbances of the kind known to occur in this disorder.

We have undertaken long-term studies on the basic biochemistry of the pigment epithelium, and recently have been able to identify the principal lipids in these cells. As shown in Fig. 5, pigment cells have an unusual (and limited) lipid composition consisting principally of 2 components, free fatty acids and lecithin. This finding suggests that, unlike most other tissues, free fatty acids play an important — though not yet understood — role in the normal functioning of pigment epithelial cells. We hope that further information on the metabolism of these fatty acids, in both normal and pathological tissues, will lead to an understanding

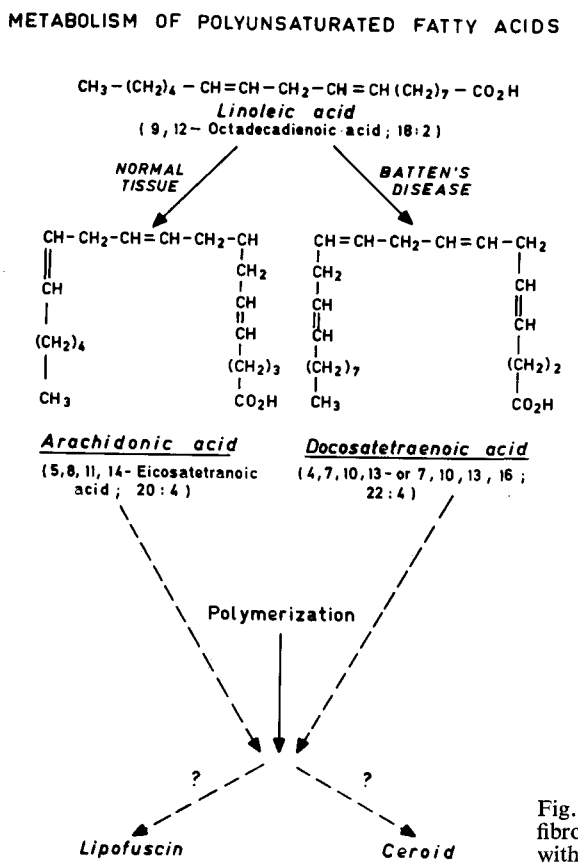

Fig. 4. Pathways of oxidation of linoleic acid in cultured fibroblasts from normal individuals and from patients with Batten's disease.

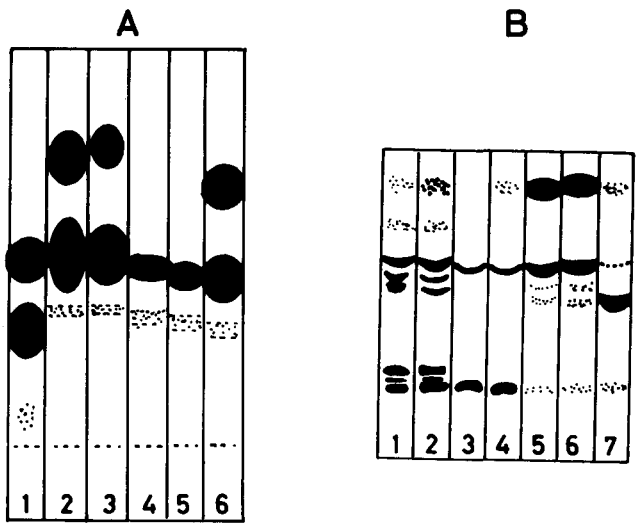

Fig. 5. Tracings of thin-layer chromatograms comparing the lipids in pigment epithelial cells with those of retina and liver.
(*A*) Chromatogram of phospholipids showing: standard phospholipids (1 and 2), and extracts from retina (3), pigment epithelium (4 and 5), and liver (6).
(*B*) Chromatogram of neutral lipids showing: extracts from retina (1 and 2) and pigment epithelium (3 and 4), standards of free fatty acids and triglycerides (5 and 6), and cholesterol (7).

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of their possible role in the pathogenesis of Batten's disease. Unfortunately we have barely entered stage 1 (see Table 1) in our understanding of this disease — or group of diseases —although there are indications of some progress in stages 2, 3, and 4.

4. OTHER TAPETORETINAL DEGENERATIONS

There are many other inherited disorders in which tapetoretinal degenerations are present. In some of them there is no clue as to the biochemical abnormality, whereas in others, we know that metabolic disturbances other than those of lipid metabolism are present. The best known of these are the mucopolysaccharidoses. There are, however, a few tapetoretinal degenerations in addition to those already discussed, in which lipid disturbances are thought

TABLE 7

OTHER TAPETORETINAL DEGENERATIONS *

	Name of disorder	Biochemical defect
I	Hooft's disease	Low serum lipids
II	Cockayne syndrome	Hyperlipoproteinemia
III	Alstrom syndrome	Elevated triglycerides and prebetalipoproteins
IV	Case described by Durand et al. (1971)	Hyperlipemia nad storage of lipids in tissues

* These disorders are considered separately because:
(*a*) too few cases have been described, or
(*b*) the biochemical evidence for lipid involvement is questionable.

to be present. These are shown in Table 7, and only brief mention will be made of them because of the limited number of cases, as in Hooft's disease (I) or the case described by Durand (IV), or because the biochemical evidence for lipid involvement is questionable (Cockayne and Alstrom syndromes).

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