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PATHOGENESIS

OF

SENILE CATARACTS.

HAROLD GIFFORD JR.
THE PATHOGENESIS OF SENILE CATARACT.

In reviewing the literature on this subject, the gross confusion in terminology and the disorder in classification is very obvious. This confusion is so great that most of the investigation and experimental work is almost valueless. One worker gives a careful discussion on the changes in blood in senile cataract but makes no mention of the type of pathology he was dealing with. In a similar manner most authors have paid little or no attention to the type of pathology, merely calling all opacities of the lens occurring after forty-five years of age, when no specific cause was found, senile cataract. This term has been used unscrupulously for a catch-all or waste basket group like the word "primary" is used with reference to the anemias, with a similar confusion resulting. The following attempts at classification will indicate the confusion. Jackson in 1907 makes no attempt at classification other than to call all senile cataracts, hard cataracts. He divides them pathologically into two classes, cortical and nuclear. The former occurring as the common type and passing through four stages; incipient, swollen, mature, and hypermature. He fails to indicate whether the four stages referred to, refer to the cortical or nuclear variety. The classification of Axenfelds in 1894 refers to them as:

- Subcapsular Cortical Cataract
- Supernuclear Senile Cataract
- Nuclear Senile Cataract

He believes the subcapsular cortical variety is the most common and divides its progress into the same four stages as Jackson. Ball in 1919 agrees essentially with Jackson. He recognizes the hard subcapsular variety as being the common senile type. DeScweinitz in 1921 divides senile cataracts into:

- Nuclear
- Cortical
- Mixed

He also mentions type of diffuse clouding in the form of small dots or blister-like bodies scattered throughout the cortex. Also a type with dark flocculent precipitates on the interior or posterior cortex, and interior capsular variety are described by him. These he does not attempt to classify.

Duke-Elder in 1937 describes cataracts as:

- Presenile
  - Coronary -- an annular zone of club shaped opacities in the outer layer of the nucleus and inner layer of the cortex (twenty-five per cent of people after puberty and very slowly progressive).
  - Dilacerated -- a thin layer of combed-out, mosslike opacity in the deeper layers of the adult nucleus.

- Senile
  - Juniform -- deep radiating plaques in the deeper cortical layer.
  - Dustlike cataract -- in the deeper cortical layers.
  - Posterior saucer shaped cataract -- confined to a single layer in the posterior cortex near the capsule.
  - Nuclear cataract -- consisting always of extremely small dustlike spots.
He continues to say that several of these are usually mixed together obscuring the distinctive characters, but makes no reference to one common type or the changes taking place in it, other than to refer to the physiological senile changes of sclerosis, discoloration, sagreen, and organic opacities formed by the coagulation of protein.

From these examples it would seem that the earlier observers recognized the common senile type of opacity formation as a cortical process, but the question now arises as to what these other forms of opacity represent and how shall they be classified? Further knowledge regarding the clinical occurrence, histo-physico-chemico-pathology, and the causes concerned in the production of these opacities, will be needed before a satisfactory classification can be made.

Before discussing any pathological processes taking place in the lens, it will be necessary to bring together the newer facts concerning the embryology, anatomy, and physiology of this structure.

**Embryology**

In embryology little knowledge has been added except to show rather conclusively that the lens arises from the surface ectoderm as a response to some stimulus, supposedly from the optic vesicle.

**Anatomy**

Anatomically however the slit-lamp and the work of Vogt on the development of the lens, has given a firm working basis for the further study of this structure. According to Vogt, and using the nomenclature suggested by Duke-Elder, the lens fibers are formed from the cells of the posterior wall of the lens vesicle, and that this makes up the entire lens until the ninth week of intra-uterine life. This is called the embryonic nucleus and shows under the slit-lamp as the "central-dark-interval." Immediately outside the embryonic nucleus, secondary fibers are laid down in layers one after the other until at birth they are seen with the slit-lamp as two kidney-shaped parts of the foetal nucleus, on whose surfaces are seen two sutures. On the anterior surface an erect Y, and on the posterior surface an inverted Y are noticeable. After birth these sutures are seen for some time immediately below the capsules, but their position becomes deeper as new layers of the infantile nucleus are laid down. Surrounding the infantile nucleus more layers of lens fibers are laid down until about the time of puberty when the adult nucleus becomes fully formed. The cortex is added in a similar manner around the adult nucleus and continues to be laid down slowly until the death of the individual. This knowledge of the development of the lens and the proper use of the slit-lamp for the location of opacities is essential in studying the development of senile cataract.

**Physiology**

The nutrition of the lens is certainly a fundamental problem associated with the development of cataract, but due to extreme specialization of the lens and its lack of any direct connection with the general circulation, makes this problem extremely complex. Even now in the light of a great mass of new facts, there is still a great deal of divergent opinion as to the source and utilization of food supply by the lens.
That the lens has an active, although rather sluggish metabolism is evidenced by the continual laying on of new lens fibers. This entails a rather constant source of nutriment, as well as a constant exchange of respiratory gases. This respiration has been observed and actually measured by several investigators and although their results are not in agreement it shows definitely that the lens possesses an active respiratory apparatus. This problem of respiration seems so fundamental and the lack of definite knowledge regarding it appealed to me as a worthy field of investigation. Following the method of Goldschmidt based, on the reduction of methylene blue as an index of the respiratory activity of the lens, an attempt was made to measure this in normal rabbit lenses, and to correlate this with the respiratory rate of cataractous lenses produced by feeding naphthalene. The results however were very disappointing and no normal respiratory rate could be established. Therefore, no comparison could be made with the respiration taking place in the cataractous lens. Schäfer says that this type of cataractous lens uses more oxygen and if this can be verified our present ideas of the origin of cataracts will necessarily be modified extensively. The work of Masahiro and Goldschmidt showed that the cataractous lens uses less oxygen and for the present this view may be regarded as acceptable.

The nutrition of the lens, on the other hand, has been the object of a great deal of study in recent years, and the mesofil material, recently brought to light by Duke-Elder and others has almost overshadowed the old and ill-founded theory of a specialized secretion from the ciliary body as being the source of nutrition for the lens. From the anatomical position of the lens it only reasonable to believe that its nutrition must come from the aqueous humor and to a less extent from the vitreous. This has never been disputed, but because of the great difference in chemical constitution between the blood serum and the aqueous, it was formerly supposed that this must represent a specialized glandular secretion. The ciliary body with its somewhat question-able glandlike structure was, in the light of no better evidence, held to be the source of the aqueous humor. Since the admirable study of this subject by Duke-Elder in 1927 I feel there is no further need to consider that the ciliary body preforms a specialized secretory function.

In brief this theory holds, "that the intra-ocular fluid is a dialyzate in equilibrium with the capillary blood", the dialyzing membrane being the capillary walls. All substances seem to enter and leave the eye by a process of simple diffusion, and their presence or concentration, while showing no evidence of any selective secretory mechanism, does conform to the physical and chemical laws that govern a simple process of diffusion through a semipermeable membrane. Obeying these laws, changes in the composition of the blood are followed by changes in the aqueous in attempting to re-establish equilibrium between the blood plasma and the aqueous humor. Although this theory is not universally accepted, it is certainly upheld by most experimental and clinical data brought out by Duke-Elder.
In accepting the theory that the aqueous is merely a dialyzate of the blood plasma it is necessary to change the conception of the circulation of this fluid to conform to this theory. The older theory of a pressure-head developed by the secretion of the ciliary body must be discarded and with our present knowledge it seems that this is only one of the many instances which have occurred in all branches of science where a conclusion, based on insufficient premises has become accepted.

It is now believed that the aqueous is essentially without a definite circulation but that due to a constant balanced hydrostatic and osmotic pressure equilibrium, and the diffusion in or out of diffusible substances, that act according to the laws of semipermeable membranes there is a circulation established. Also there is a pressure circulation produced by the action of the internal and external musculature and pulse beat which must be considered as influencing the movement of the aqueous. This however is secondary and in general circulation is governed by the greatest outward diffusion from the highly vascular ciliary body. Any change in this pressure will be transmitted throughout the aqueous which will find an exit far down the venous pressure gradient at the canal of Schlem. The old idea of the direction of circulation which has been substantiated by clinical and experimental evidence is still accepted, but the method of its production has changed to meet the theory of dialization.

In studying further the nutrition of the lens the function of the lens capsule must be considered. Although little work has been done on the physiology of this structure I feel quite certain, that from the investigations of Friedenwald on this structure, that the capsule may be considered to act as a semipermeable membrane governed by the physico-chemico laws of diffusion. Some of these laws with special reference to the lens and the capsule as representing a physico-chemico system separate from the aqueous, have been considered by Duke-Elder. The chemical composition and osmotic value of the lens is widely different from the aqueous. Also owing to the tonic pull on the capsule by the ciliary muscle the external tension of the lens is kept at a higher level than that of the aqueous and therefore while fluid may pass out by filtration and diffusion it can only enter by osmosis.

The importance of the lens capsule in maintaining this physico-chemico balance is obvious and Friedenwald has recently begun a series of investigation concerning the function of this structure.

He has shown that the capsule possess no pores of microscopic size and that it takes no negative electrical charge in sodium chloride solution. The permeability is qualitatively the same in vivo as in vitro and is permeable to all electrolytes, solutes, and small colloids and differs little between species of animals. Friedenwald has also shown that its permeability in vitro is decreased by calcium cyanide and proteins and also in the older animals. These general facts have not been confirmed by other investigators and because of the difficulties encountered in working with such a small membrane, they should not be accepted without reservation.

Since the fundamental changes in the formation of opacity is now considered to be the coagulation of the lens protein, a brief resume of their nature and function is essential to the understanding of opacity formation.
The lens protein have been investigated by Lapschinsky (1878), Morner (1894) and more recently by Jess, Goldschmidt, Tassman and Woods. From a review of these works the proteins may be considered to be four in number: "Albumoid", a water insoluble protein found especially in the nucleus; two water-soluble proteins found especially in the cortex, Alpha and Beta Krystalline; finally albumin found only in small quantities. In discussing the action of these proteins it will be necessary to understand the fundamental chemical reactions involved in lens metabolism. The work of Jess (1880), Goldschmidt (1897) and Adams (1925) and Hopkins and Kendall in biochemistry have brought out many new facts about this subject. Since the work of Arnold in 1912, on muscle metabolism, it has been known that the presence of cystine is correlated with active metabolism. Around this substance containing an SH radical and a high percentage of sulphur, an internal auto-oxidation system of the SH -- SS type was gradually worked out by Paulhorste, Thunberg, Heffer. This system Goldschmidt in 1917 felt might play an especially important role in lens metabolism because of the lack of blood supply in this structure. Following the discovery of Hopkins in 1921 of a sulphur containing compound isolated from yeast which he thought was a dipeptid of glutamic acid (glutathione), Goldschmidt demonstrated this substance in the lens. The further work by him and by Adams in 1925, established the connection between glutathione and lens metabolism. They showed that its presence is essential to respiration. It is now generally accepted that there is present in the lens as in other tissues and auto-oxidizing system in which glutathione plays a leading role. In brief this system in the lens may be considered to function with glutathione acting as a hydrogen donator which reduces the hydrogen acceptor and Beta Krystalline acting as a thermo-stable residue which reduces the glutathione after it has been oxidized. The avascularity of the lens raises this internal auto-oxidative metabolism to a primary importance and it would seem to follow that slight dysfunction of this system might jeopardize the life and transparency of the lens fibers. The relative importance of this internal auto-oxidation system and the external respiratory system utilizing oxygen is not all clear, but it is quite obvious that the formation of opacity is in some manner closely associated with a dysfunction with one or both of these systems.

Before taking up the pathological changes occurring in cataract formation it may be well to analyse further the physiology of the lens as it is understood at present. The primary function of the lens is to transmit light and focus it upon the retina. To accomplish this the lens must retain its transparency and elasticity. Its elasticity normally decreases with advancing years by a process of sclerosis. Along with this there is also an increase in the density of the lens fibers with a subsequent change in their refractive index. But since this does not interfere with the acuity of vision it cannot be considered a pathological process. This sclerosis of the nucleus and older fibers and the deposition of new fibers forming the cortex is continuous throughout life and has been observed carefully by R. Von der Heydt. He says
that by virtue of this change the nucleus zone gradually becomes more condensed and the lens flatter. This condensation of the nucleus results in a higher refractive index which seems nearly to neutralize the flattening of the lens and maintain a normal refraction of the eye throughout life. Von der Heydt describes definite physiological changes in the lens that take place about the time of puberty, "a lamellar layer in the middle of the cortex becomes sharply demarcated and presents a luminous surface-contour-reflex." The lens within this zone was called by Vogt the "Alterkern". (Adult nucleus) Von der Heydt continues to say that in age the surface luminosity of the adult nucleus is often so marked that it gives the lens a grayish appearance which has been mistaken for cataract. This peculiar differentiation in the cortical lamellar structure, however, does not interfere with the transparency of the lens nor with visual acuity."

That this process of sclerosis may not at times advance to the point where transparency is impaired is not denied, but I feel certain that with this advanced sclerosis there is an associated beginning coagulation of the proteins.

Until now this discussion has been limited so far as possible to the presentation of known or well established facts relative to the structure and function of the normal lens. In summarizing these newly acquired facts, and after a careful analysis of these findings, the lens may be considered as epithelial structure arising from the ectoderm under the influence of the optic vesicle. It may be said to have besides an external respiratory system an internal metabolism in which glutathione and Beta Krystalline play important parts. Its nutrition may be considered to be maintained by a finely balanced physico-chemical equilibrium established between the lens and blood stream by means of the aqueous humor. The walls of the arterioles and the lens capsule are thought to act as semipermeable membranes. The lens also undergoes a certain physiological sclerosis with advancing years. It is by studying the disturbances in structure and function that a better understanding of the pathogenesis of senile cataract may be obtained.

**Pathology**

The uniformity and simplicity of the structure of the lens should make the study of its pathology a relatively easy subject. But in spite of this simplicity of structure there has been a great deal of difference of opinion as to the changes taking place and the causative factors involved in the pathogenesis of the cataract. It is now quite generally agreed that the formation of all opacities in the lens is essentially a coagulation of the protein constituents of its fibers. In the words of the Germans it is merely a "Koagulationsnekrosen." As Friedenwald states it, it is simply death of tissue resulting in coagulation and followed by calcification and lipid in filtration. This is merely a fundamental biological reaction common to all tissues resulting from injury of some sort. Although this does limit the pathological changes in the lens, coagulation of protein in itself is complex and poorly understood process and must be considered in detail.

According to the most recent ideas proteins may be changed from the colloidal to the particulate form by two distinct processes, precipitation and coagulation. Precipitation, which is brought about by the action of concentrated salts as ammonium
sulphate, or by alcohol, is a reversible and purely physical change whereby aggregates of chemically unchanged particles are thrown out of colloidal solution in a condition capable of reversion to their original colloidal state. With this we are probably not concerned in the development of cataract. On the other hand is a complex process which takes place in two stages: (1) Denaturation, whereby the natural protein is altered to a form in which it is readily coagulable. (2) Agglutination, a physical process whereby coagula are formed by flocculation of the denatured particles. The intimate nature of the primary chemical change of denaturation is not yet cleared up, however, Harris (1923) has brought out evidence to show that it is probably hydrolysis involving the production of a sulph-hydryl group from the thiopetid linkages. In the development of cataracts a considerable amount of hydrolysis of this type takes place, as is shown by the finding of deposits of tyrosine, in the aqueous. (Burdon-Cooper) The discoloration of the black cataract is considered to be due to deposits of melanin, an oxidation product of tyrosine. The ordinary yellow discoloration in the senile non-cataractous lens may thus be considered as the result of hydrolysis indicating that this process is to some extent taking place, although the transparency is not impaired. In the usual course of events the two processes, denaturation and agglutination take place almost simultaneously, but they may be separated by a theoretically infinite duration of time. The influence of radiant energy may induce denaturation over a long time interval, and the denatured protein remaining unagglutinated, leaving the medium of which it forms a part, transparent until such time as suitable conditions induce flocculation and consequent opacity. Mond (1922) has shown that after ultra-violet irradiation such as will not produce agglutination, proteins showed definite physical and chemical changes and exhibit a decrease in stability becoming more labile and more readily coagulable by various agencies.

In discussing the factors capable of producing coagulation they will be taken up with their association to the production of cataract in general. Later these factors will be evaluated in an attempt to analyze their importance and mode of operation in producing senile opacities. These disturbing influences may in general be divided into three classes: Mechanical, Chemical, and Biological factors. Although eventually their effect is to produce coagulation of the lens protein their origin may be exogenous as radiant energy and trauma, or endogenous as toxic and metabolic disturbances. Further, these influences may be associated with local changes in the eye as capsule permeability, or with general disturbances in the body as a whole as senility. Also these factors become inter-related in such a complex manner that any strictly orderly classification cannot be made. Merely for convenience these factors may be discussed as (1) those arising from or producing local changes. (2) Factors arising from changes in the entire organism.

Local Changes.

These local changes may again be roughly divided into mechanical, chemical and biological changes. Of the mechanical factors, trauma has long been known to produce cataract. Rupture or even slight damage to the epithelium of the capsule as capable of producing opacity of the underlying fibers or of the lens as a whole.
The degree of opacity roughly corresponding to the extent of the injury. If the injury is slight, as in the passing of a small bit of steel no reaction of the lens as a whole takes place. If the injury is more extensive a local proliferation of the epithelium and a slight subcapsular opacity usually results. But in some cases even relatively slight injury to the capsule is capable of producing an opacity of the entire cortex. If the injury is very severe and a damage to the capsule extensive the entire lens becomes opaque, disintegrates, and in time is absorbed leaving an aphakic-eye and these sclerosed remnants of the capsule.

Another physical factor, radiant energy in all its forms, (heat, cold, ultra-violet, infra-red and X-radiations, and visible light) has been shown by Duke-Elder to be intimately associated with the formation cataract. He has review the literature carefully, and with only a few exceptions, accepted the work of others after it has been confirmed by further investigation. Since this article was written new factors have been discovered concerning the fundamental reaction taking place in the lens, but on the whole these would modify his theory but slightly.

Some of the evidence collected by Duke-Elder and his conclusion will be summarized in an attempt to evaluate the effects of radiant energy as a factor in producing opacities of the lens. Light as it is commonly considered is merely a source of radiant energy, and includes all wavelengths above and below the visible spectrum. All radiations transfer energy to the substance which absorbs them, and these substances react to a greater or less degree depending how readily radiant energy is absorbed. Apart from this general effect of producing molecular motion considered as heat, photo-chemical, and photo-electrical, there is no evidence of any specific action peculiar to any wave length. It can be shown that the lens is reached by certain limited radiations between definite limits. The absorbed rays are the only ones that need be considered as these only can produce the action in the lens substance. However, due to dispersion and reflection in effectual wave lengths may be varied so that they produce effects. In general the absorbed rays are those coming within the range of the short infra-red, visible, and the long ultra-violet rays as well as a high percentage of X and Gamma rays. It has been shown experimentally that ultra-violet rays and X-rays are capable of producing cataract, and the clinical finding of cataract in glass blowers, X-ray workers etc., upholds these findings.

The action of radiant energy on the lens capsule can be seen experimentally and is divided into thermal and abiotic effects. The longer wave lengths produce tissue death by coagulation of the proteins with a subsequent exfoliation of the cells. When in sufficient intensities, Jess has shown that the shorter wave length produce a typical abiotic effect. Great intensities cause the cornea to become opaque and this protects the underlying structures, while lesser exposures the factor of physiological repair comes into play in the interval. After short exposure a swelling of the cells is the only change noted. Further intensities involve the appearance of typical eosinophilic and lymphatic cells associated with the abiotic reaction are seen. More prolonged exposure produces nuclear pyknosis. At the periphery of the exposed zone just under the pupillary margin there is a zone
of cellular proliferation surrounded by an area of karyokinetic activity. This may be considered to be due to stimulation from the thermal effect increased by the greater absorption of light by the retinal pigment which comes at a close association with the lens capsule at this point.

With regard to the lens substance the histological evidence of injury is much less obvious. The lens substance in a narrow region just underneath the capsule is the only tissue markedly affected. Here the staining is much less differentiated, the architecture of the fibers becomes blurred, and they themselves become swollen, losing their orderly arrangement. Some of the more superficial fibers are separated by clefts, and the capsule is frequently separated from the lens substance. In the interior of the lens changes are evident, that seem to be localized to the radiated area. These changes are typically abiotic but in no case was any fragmentation or disintegration of the fibers observed.

In discussing these findings Duke-Elder concludes that the subcapsular damage is so slight as to be of little importance while the chemical changes in the nucleus are perhaps of more significance. These changes are probably of a physico-chemical nature affecting the auto-oxidation system upon which the tissue depends for the continual continuation of its metabolism, and altering the lability of the lens proteins rendering them more susceptible to subsequent coagulation by other influences.

Among the other influences referred to by Duke-Elder, the purely physical phenomenon of osmosis should now be considered. The importance of this process in maintaining the nutrition of the normal lens has been previously referred to. This normal mechanism may be disturbed in several ways; (1) if the differences in osmotic pressures between aqueous and lens is increased; (2) if the internal tension of the lens is lowered, or the intraocular tension is increased; (3) if the permeability of the capsule is altered. Clinical evidence that alteration in the osmotic balance is capable of producing cataract is plentiful. In diabetes where the concentration of the blood sugar is raised, the lens seen to take on fluid, swell, become myopic, and droplets appear beneath the capsule. This interferes with transparency by unequal refraction and by the dispersion at the interface of fluid and lens fibers. This abnormal fluid traffic if allowed to persist will eventually lead to opacity formation, but if the hyperglycemia is controlled a reversal of the process takes place and the lens again becomes transparent. This apparent paradox of a hyperglycemia producing an inflow of fluid into the lens is explained by simple physical laws brought out by Duke-Elder. He shows that due to the increase in blood sugar there is in reality a decrease in the osmotic value of the blood, and tissue fluid, brought about by an increase blood volume through dilution and decreased blood salt. It is obvious from our knowledge of the normal osmotic processes taking place in the lens that with a decrease osmotic value in the fluids bathing the lens, water will tend to flow into the lens to re-establish equilibrium or the soluble constituents as the albumin and electrolytes will diffuse outward. That the former process is more active in this condition is shown by Burdon-Cooper who finds little tyrosine in these cases.

An example of the second manner of altered osmotic tension
is seen in the cataracts of absolute Glaucoma, where the intraocular pressure is raised above that of the lens system. Other nutritive factors may also enter into this condition but osmosis is undoubtedly the chief factor. Further changes in the osmotic tension have been pointed out by Burdon-Cooper. His study of the surface tension of the aqueous in senile cataract, which he took as a measure of the osmotic value, showed that this tension approached that of water more than the normal aqueous. Under these conditions there would be an attempt to reach an equilibrium either by the influx of water to the lens or an abstraction of the soluble proteins or electrolytes depending on the preferential permeability of the lens capsule. The effects of pathological states of accommodation may also be considered as physical changes and would come under the head of altered osmotic balance as the pull or relaxation of the ciliary muscle would regulate the internal tension of the lens.

Conditions of hyperopia were considered to be more important because of the greater accommodation necessary for its correction, and the adverse influence on the ligaments and capsules. The explanation given by him is that in these cases there is also an oblique astigmatism resulting in irregular torsional accommodative efforts producing an irregularity in the shape of the lens. This constant mechanical strain on the lens fibers could in itself produce a denaturation of the lens proteins and if continued or other factors of disturbed osmosis become manifest the result would be corneal opacity formation. Therefore, gross errors of refraction, especially when associated with astigmatism should be recognized as the causative factors in the production of at least one type of cataract, and may act as a contributing factor in senile cases.

In discussing the altered permeability of the capsule it would seem simple to say that its permeability may be varied in three ways. It may either increased, decreased or its preferential permeability altered. This latter change is exemplified by the loss of potassium found in cataractous states. The fallacy of saying that this loss of potassium is therefore evidence for preferential increase in permeability to potassium is obvious in that it is equally reasonable to say that it is due to a decrease in preferential permeability or merely to a general decrease in permeability not allowing the normal store of potassium to be replenished. In a similar way a finding of the decrease or absence of glutathione in cataracts can therefore not be said to be due to an increased permeability allowing these substances to be diffuse out of the lens, as it is just as likely that it would be found absent if there were a decreased permeability to the entrance of glutathione. In evaluating this finding and also that of Goldschmidt that there is a loss of the soluble proteins they must be considered as due to an altered permeability of the lens capsule or since one cannot think of an increased permeability allowing these substances to pass out without allowing them to pass back with equal ease the permeability may be said to be decreased. In this manner the disappearance of these substances is based on an inability of the lens to replenish its normal supply, and continued metabolism exhausting that normally present.
If any statement regarding absence or loss of a substance normally present in the lens is to be made, it seems much more in line with the physical laws concerned with permeability to say that there is an altered permeability and if the work of Friedenwald is considered who finds a decreased permeability with age this alteration of permeability this may also apply to general changes in the lens capsule. The possibility that the metabolism of the lens has become altered to such an extent that these substances are no longer needed must also be considered as responsible for their absence.

Friedenwald was able to produce cataracts by injecting successively eosin and Gentian Violet one per cent, in normal saline into the vitreous of rabbits. This produced a precipitate on the posterior capsule which was shown in "vitro" to decrease the permeability only slightly but definitely to certain substances. The conclusion was drawn that only a slight change in the permeability of the lens capsule is required to obstruct the metabolic processes of the lens sufficiently to cause cataract.

Friedenwald feels that these experiments justify the statement of a theory that some forms of senile cataract are cause by an exaggeration of the decrease in permeability which normally takes place with advancing years. The validity of these statements has yet to be confirmed but that an altered permeability of the capsule is an influencing factor in the formation of cataract cannot be disregarded.

A resume of the mechanical factors known to be associated with the production of opacity include, beside trauma; radiant energy; altered osmotic balance; and altered permeability of the lens capsule. At present the operation of the factors in the production of the senile type of cataract is not fully understood, but I feel that after an analysis of the chemical and biological changes taking place in the lens, an attempt may be made to evaluate the importance of each, and that some conclusion may be reached regarding their mode of action.

It is along biochemical lines that the greatest advancement of our knowledge concerning the genesis of cataracts has been made, and it seems likely that it will be along these lines that a final solution to this complex problem will be reached.

For the most part chemical changes in the aqueous are closely associated with those in the lens, but so far experimental evidence has shown that the hydrogen ion concentration remains fairly constant at 7.3 to 7.5 and that in cataractous conditions it is invariably alkaline. This with the inability of the aqueous to maintain a high degree of molecular concentration, due to rapid diffusion into the blood stream does not allow the salt concentration to reach a point where it could cause opacity formation, either directly or through increasing acidity. The sensitization effect of these salts and the coagulation of protein may be affected. Calcium glucose and aceton have all been shown to accelerate the rate of opacity formation under the influence of radiant energy, and Adams (1936) showed the sensitization affect of
glucose in the production of cataracts in rabbits by feeding naphthalene. This sensitization effect cannot be disregarded in studying the occurrence of senile cataract in the diabetic which evidence has shown to be a rather frequent happening, although the true diabetic type of cataract is rare.

In discussing the chemical changes in the lens proper, it will be remembered that the substance glutathione and the Alpha and Beta Krystallines are considered of primary importance to the internal metabolism of the lens. Also the amino acid, tyrosine and its oxidation product melanin, which Burdon-Cooper has shown to arise in the lens from the hydrolysis of protein may be considered as indicating the breaking down of the lens protein.

First, during the normal process of senile sclerosis, the fibers of the nucleus are changed from a soluble albuminoid, becoming homogenous without fissures or granules. Further it is generally agreed that there is also a gradual color change from light amber to brownish red, which in some cases becomes black (catactica nigra). Under usual conditions no opacity is formed, the loss of the visual acuity being due to absorption of the shorter wave lengths of light because of the increasing density of the lens nucleus. Friedenwald in 1929 attributes the color change to a purely physical phenomenon of absorption, while Burdon-Cooper has shown quite conclusively that hydrolysis of the lens proteins is taking place. This is shown by the presence of tyrosine. The discoloration being due to an oxidation product which Burdon-Cooper believes is carried out by an oxidase in the lens.

Further study by Burdon-Cooper shows that the cataracts from India are more deeply colored than those from European Nations, and concludes that light is necessary, an altered chemical change (hydrolysis) preceding the development of the tint, that the tint would appear to be a protective mechanism and is undoubtedly an expression of a retrograded phase in the life of the lens.

The discovery by Ries, 1912, that the cataractous lens was lacking in that cystein containing compound, now known as glutathione, gave a new stimulus to the work. The absence of this substance indicated that the internal metabolism of the lens was definitely disturbed. Jess showed that his Beta Krystalline was particularly rich in sulphur, and that this compound was decreased or absent in the cataracteous lens, along with a slight diminution of the Alpha Krystalline. He also showed a general tendency for these Krystallines and water to decrease with age, while the albuminoid content increased. These findings would all point to a disturbance in the auto-oxidative system in the lens. Adams has shown a similar disturbance of this system in the naphthalene cataract as indicated by the absence of glutathione in these lenses.

My own work with naphthalene cataracts showed that although there was a marked diminution of glutathione which became more apparent as the degree of opacity increased, there was still a measurable amount present even after the opacity had persisted for nearly a year. The absence of this substance was also noticed in traumatic cataracts, but considerable time was necessary for its complete disappearance. From the work of Jess, the disappearance of the reactive Kd group has been found to take place only in that part of the lens which has been opaque for some time. Therefore, in the incipient senile cataract, the nucleus only lacks the cystein reaction as shown by the Sodium-Nitro-Prusside test, while in the mature cataract this reaction is absent except for a small rim at periphery of the cortex. In the traumatic type at first this
reaction is present throughout the entire lens. Later the reaction becomes faint in the center and finally disappears except for the ring at periphery. In the naphthalene cataract this reaction is lost first just surrounding the nucleus and disappears gradually towards the periphery as the opacity becomes older.

Further studies by Hopkins indicate that the Sodium-Nitro-Prusside test is an indication of reduced cystein (SH) and may be considered as a measure of thermo-stable residue or the Beta Krystalline of Jess. This reaction, I found to remain positive in ground and acid extracted lenses which showed a marked decrease in glutathione and were completely opaque. This finding and the extended time necessary for the disappearance of this cystein reaction in traumatic would seem to indicate that although opacity may be well advanced or complete, the active elements in the auto-oxidative system are still present in measurable amounts. From this it would seem that the loss of glutathione and the disturbance of this system is not primarily the cause of the formation of the opacity but rather the dysfunction of this system is secondary to the formation of the opacity or the factors bringing on the changes in the protein, which is recognized as cataract.

This is not the generally accepted manner of explaining disturbances of this auto-oxidative system. Damage to it by some unknown factor usually considered to be toxic or nutritional, has been in recent years accepted as the cause of the opacity, but I prefer to think of these altered chemical reactions as merely the result of the coagulation and that some other factor is to be looked for as bringing this about.

The other chemical changes in the cataractous lens are not so well established. The diminished amounts potassium has been referred to already, but the explanation of this change is not clear. No reference could be found as to the concentration of this substance in the blood of patients with cataract, but a certain amount would be necessary for the organism to maintain life. Its deficiency therefore in the cataractous lens may be considered as a lack of demand by this structure or an inability to utilize potassium in its disturbed chemical state.

With regard to the lipoid substances there is a great deal of disagreement as to whether they are increased or decreased in cataract. Gross has found no increase in lipoid content in either the senile or cataractous lens, while Burdon-Cooper finds an increase which he attributes to the hydrolysis taking place in the cataractous lens. Goldschmidt found that these substances were at a minimum between the ages of forty to sixty, and that in the cataractous lens they are withdrawn from solution and therefore, from activity and deposited as crystalline and amorphous particles, which may be macroscopically evident. Until further work has been done along this line the general opinion is that the lipoid content is increased, due to a fatty infiltration of the dead tissue and in a like manner the increased calcium is thought to be due to a process of secondary classification.

In summarizing the chemical change in the lens the important disturbances may be said to be, besides the presence of tyrosine, an increase in the albuminoid constituents with a decrease in water and Krystalline making the lens as a whole smaller and lighter. Also there is a marked decrease in glutathione and Beta Krystalline and potassium while the calcium and lipoids are thought to be increased.
Biological Changes in the Lens.

Biological changes may be limited to disturbances in the enzymes, and ferments or immunological reactions taking place in the lens. The very nature of this subject will be evidence enough to indicate the lack of information concerning these reactions. However, work along these lines has not been altogether unfruitful and further work may bring out many important factors that so far have obscured the clear understanding of this complicated process of opacity formation in the lens. Goldschmidt (1914) demonstrated the presence of a proteolytic ferments in the aqueous. He says it is conceivable for these protein bodies being water-soluble, to be broken down by a fermentation process more quickly than the albuminoid. The cell ferments are liberated with the initial cellular death and go on to decompose the cell further into many fragments. The end products could some form of amino acids which could pass undisturbed over the lens capsule and be taken up by the intraocular fluid. In nuclear cataracts the initial destruction would have to effect some inner lens fiber. The plausibility of this hypothesis seems slight in the newer light regarding the coagulation of proteins, but the presence of this enzyme and the oxidase believed to be present by Burdon-Cooper should not be forgotten. The variability of these substances may in some way explain the formation of opacities in one individual when opacity does not develop in another under apparently similar conditions. This individual variation was noted in my own work with naphthalene cataracts in rabbits. Of twenty rabbits, fed under similar condition, two failed to develop opacity other than a few superficial redial stria, even after three weeks of a daily administration of a dose of naphthalene that in other rabbits produced opacities on the fourth day which progressed to complete maturity with no further dosage. Findings such as this can only be explained by individual biological variations, and are frequently seen in general therapeutics.

The organ-specific immunological reaction of the lens has, however, become well established since the work of Uhlenhuth in 1903. This same organ specificity and the anaphalactic reaction produced in the sensitized individual by his own lens protein applies to the cataractous condition also. That this reactivity is especially associated with the Alpha and Beta Krystalline was shown by Dolt and Flosener. (1928) Romer and others have advanced the theory regarding specific cyto-toxins produced by the individual having specific affinity for lenticular antigen. Lens anti-sera have been prepared and believed by some to have a therapeutic use in retarding the progress of cataracts, but these have met with more or less failure. Until more definite facts are known about the immunological reactions in general, nothing definite can be said regarding these factors in the production of cataract.

Changes in the Body as a Whole.

The fact that senile cataract occurs invariably in both eyes would at once suggest that its cause should be found in some dyscrasia or metabolic disturbance of the body as a whole. This idea has been prevalent since earliest times as the therapeutics of senile cataract indicate, and though the value and the methods of therapy have changed, the importance of a general systemic conditions in the pathogenesis of senile cataract still retains its place as the primary factor leading to opacity formation. These systemic changes in the body may be grouped con-
veniently under three heads: Senile Change; Endocrine Dysfunction or disturbed metabolism; Toxic Conditions. In discussing these changes they are so closely associated that it is impossible to separate them distinctly.

It is very difficult to say definitely what constitutes senile changes in the body. Senile Change implies degeneration and dysfunction, but these are also the result of disease and impaired nutrition. Faulty nutrition followed by degeneration and loss of function undoubtedly occurs as a result of sclerosis of the vascular system. But can this sclerosis be considered in normal senile change or is it the result of disease? This question has yet to be settled, but until that time the old adage "A man is as old as his arteries", still seems applicable.

Age in itself is no indication of senility, while the signs of degeneration are definite indications of the ageing of the individual. That these signs may appear at forty years in one individual and not until eighty in another is recognized. The appearance of these signs of degeneration may be said to be governed by the idiopathic predisposition of the germ plasm for that particular cell, organ, individual, species, or race. This is essentially determined by heredity in dealing out a physical organization of varying capacity for development and life, but this previous position in the final analysis is controlled by the environment to which it is subjected. Therefore, in the individual any predetermined capacity for life comes under the influence of the vascular system. It is in this system then that we may expect to find the senile changes that determine the continued activity or degeneration of an organ or organ part.

With reference to the changes in the lens, arterio-sclerosis and its accompanying hypertonic have been shown clinically to play only a minor role if any in the production of opacity. Fraenkel on the other hand, believes degenerative changes in the organs of the body, determined by their idiopathic constitution or their state of nutrition, due occur, and the result of the regressive metamorphosis will be reflected in the metabolism of the body as a whole and in the composition of the blood. Besides the liberation of the products of disintegration whose toxicity may be considered to be a variation of the ability of the organism to eliminate these waste products, in which the kidney becomes an important factor, degeneration of the endocrine glands with the production of an altered metabolic state, must be considered as factors in the production of cataracts.

In an attempt to correlate this altered metabolic state with formation of cataract extensive studies of the blood chemistry have been undertaken. In general these findings point to an increase in the serum calcium. Fischer and Tricbstein, however, have suggested that a low serum calcium associated with a parathyroid deficiency and latent tetany in eighty-eight per cent of their patients is present in those suffering from senile cataracts. Other results were variable, and although Adams in experimental naphthalene cataracts showed that an increase in the serum calcium did not effect the formation of the opacity, she did show later that there is a lowered serum calcium intoxicated with naphthalene. Also the clinical findings of juvenile cataracts in individuals with manifest teteny, and the experimental production of cataract in parathyroid caesinized dogs by Hiroshi, would in-
dicate that disturbances in calcium metabolism is in some way associated with the production of cataract. The status of blood cholesterol is also rather vague. O'Brien found an increase in fifty per cent of his cases of senile cataract. Fat in fifty-six per cent and leucithin in seventy per cent was found to be increased. Both Adams and Michael have found a slight increase in blood cholesterol in the earlier stages of naphthalene intoxication, which later returned to normal or below. Adams suggested that when this rise was slight the opacities appeared sooner and progressed to a more marked degree. This would suggest that the hypercholesterinemia acted as a protective mechanism. The work of Michael and Vancea would seem to show that there is an associated dysfunction of the supra-renal cortex in naphthalene intoxication. The stimulation of the autonomic nervous system by them produced a moderation of the effect of the naphthalene, which was thought to be due to an exaggeration of the protective mechanism. Also blockage of the reticulo-endothelial system by intra-venous injection of Carmine Lithium Oxide produced an exaggeration of the toxic effect of naphthalene through inhibiting the production of cholesterol for protective means. These experiments have not been repeated but until confirmed or disproved the hypercholesterinemia may be regarded as a protective measure. This inter-relationship of the supra-renal glands, autonomic nervous system, and cholesterinemia does exist and should be considered in the pathogenesis of senile cataract.

O'Brien has shown that eighty-two per cent of his patients gave a high fasting blood sugar level, and also seventy-two per cent gave abnormally high sugar tolerance curves, indicating an inability properly utilized glucose. The association of senile type of cataract with the diabetic state is generally recognized, and although it has been shown by Burdon-Cooper that the sugar level is not in itself a cause except in the true diabetic form associated with the preliminary myopia, the production of specific cyto-toxins as products of deranged metabolism, and the sensitizing effects of glucose and acetone on the lens proteins, may be considered as definite factors in the production of opacity in the lens.

In observing further the chemical changes in the blood of senile cataract there seems to be accumulating evidence that there is a retention of nitrogenous matter in the blood stream, although clinical evidence shows no obvious kidney insufficiency in these patients. O'Brien found an increase of uric acid in seventy-seven per cent of his patients, and an increase of urea-nitrogen in thirty-nine per cent. In these cases there was no obvious kidney pathology. Grilli in studying the urine of cataractous patients noticed a lowered osmotic pressure value and a raised freezing point. From this he concluded that there was a diminution of toxicity of the urine and that cataract occurred in individuals with senile kidney. Along these same line Fraenkel after a study of the efficiency of the kidney of the cataractous patient, concluded that the kidney does not eliminate in the ordinary way toxic products elaborated by the organism, but that this inefficiency had no appreciable effect on the general circulation. This inefficiency referred to by Fraenkel is only demonstrable by cryoscopic methods. Burdon-Cooper adds evidence of a renal insufficiency by the finding of increased amounts of tyrosine in cataractous patients with definite kidney pathology. He observes that the presence and accumulation of cyto-toxins in the organism
is probably a constant physiological process and takes place without detriment to the lens unless there is inefficient destruction or elimination of these toxic products. The influence of heredity in determining the capacity of the cells to produce the cyto-toxins is probably primary, but only reaches this importance when associated with kidney insufficiency.

The effects of general debility and cachetic states on the body as a whole has been correlated with cataract formation. I feel however that this is not due to any specific change in the tissues or body fluids, nor can it be said to be due to the lack of nourishment produced by such debilitated states. If this were true cataract would be three or four times as common as it is at present. I do believe that the cataract found to develop occasionally under these conditions, is the result of failure of the normal protective mechanism such as active elimination, failure of the normal protective mechanism, loss of vitality of the capsule, linked with pre-existing local changes in the eye. Although there is little proof of this statement the relative rare occurrence of cataract under these conditions would lead one to search for an underlying cause, the debility acting merely as an exciting factor.

The subject of general body toxemia has been fairly well covered in the previous discussion, and the frequent references that have been made to the cataract produced by naphthalene intoxication indicate the importance of this factor in the production of cataract. The appearance of opacity in the cortex where vitality is relatively high would point to a toxic cause of the disturbance rather than faulty nutrition which would act first on the less vital fibers deeper in the nucleus.

Although cataract has been produced by a variety of toxic substances as naphthalene, quinoline tartrate, tin mercury and strontium, no specific toxic factor has been found to be the causative agent. It seems that although the animals give little evidence of intoxication, a general bodily change is produced. The low blood calcium and raised cholesterol content as well as the maris polyuria which I noticed in my experiments with rabbits would indicate a general body disturbance. Along with the lenticular opacities and usually before their appearance retinal changes are also manifest. There are also changes in the vitreous with the deposition of inorganic crystals. A decrease in the glutathione content and the protein fractions, Alpha and Beta Krystaline was also noted by Adams. From these findings the opacity has been considered to be the result of the disturbed auto-oxidative system subsequent to an altered permeability of the lens capsule produced by some toxic product of the naphthalene. Since no toxic has been isolated and from a study of the cystein reaction, I am inclined to believe that the changes in the auto-oxidative system are brought about by some cyto-toxin produced by a disturbed general metabolism under the influence of naphthalene or other poisons. The close resemblance of this toxic opacity to the cortical senile variety would not only indicate that the senile type is toxic in origin, but that further knowledge concerning the production of this toxic cataract would aid materially the study of the senile variety.
The production of cataract by poisoning with ergot presents still another approach to this problem, but since experimental work has been done along this line and its clinical occurrence is rare this type will not be discussed.

The importance of focal infection has been emphasized in recent years and according McCullan every case of lenticular opacity was found to have a condition of focal sepsis, usually teeth, tonsile, or accessory sinuses. It is impossible to evaluate properly such a statement, but if focal infection is a factor the recent onslaught on focii by the surgeons should certainly reduce the incidence of senile cataract. The possibility of such focii as being the source of some toxic product capable of injuring the lens or its capsule should not be passed over lightly, but it will require a great deal of work on this controversial question before its importance can be established. In summarizing the general bodily disturbances that are associated with the production of opacity, it is readily seen that in general it may be said to be metabolic, the result of senility, endocrine dysfunction, disease or toxins. The complex inter-relation of these factors along with the renal inefficiency and local changes in the lens, is obvious.

Pathogenesis.

Having discussed the changes taking place in the lens and surrounding structures and the changes in the body as a whole with reference to formation of opacity in general, an attempt will now be made to analyze these changes and the factors producing them with reference to the pathogenesis senile cataract.

The types under discussing are limited to the cortical or subcapsular variety and the nuclear type. The infrequent occurrence and lack of knowledge concerning the perinuclear and punctate forms makes a discussion of these forms impractical at the present time.

The pure nuclear variety as I have previously suggested seems to be merely an exaggeration of the process of nuclear sclerosis, the loss of visual acuity resulting from the progressive increase in the refractive index and the subsequent absorption of the shorter wave lengths of light. This sclerosis may however be considered pathological in that it is excessive and the presence of tyrosine, the oxidation of which gives the lens its reddish hue. This hydrolysis takes place very gradually and is limited to the sclerosed nucleus. The cortex remains clear except when the sclerosis has progressed to involve this structure in which case a black cataract is produced. The possibility of cortical involvement being superimposed on this nuclear variety no doubt does occur and has led to much of the confusion regarding the nuclear cataract. When cortical opacity occurs it is most likely due to some of the factors producing opacity in general, and should then be considered as a cortical cataract even if the nucleus is also markedly sclerosed.

In analyzing the factors producing this nuclear type, local changes in osmosis and permeability (the decrease referred to by Friedenwald excepted) would be ruled out because of the location of the primary lesion in the center of the lens. For a similar reason general systemic changes in metabolism, endocrine
dysfunction, and toxemias could not enter as a causative factor as their influence is made possible only by way of the blood stream, aqueous, and capsule, and produce capsular or subcapsular damage first. Chemical changes acting as a disturbance in the auto-oxidation system undoubtedly take place, but this is felt to be only secondary to some other causative factor. This other factor than, by this admittedly unsound process of reasoning, must be radiant energy. This we have shown as capable of producing hydrolysis of protein, which under the influence of the sclerosis becomes more effective. The other great factor, senility, when linked with radiant energy may be said to be the primary factors in production of this type of cataract.

In evaluating the importance of these factors, radiant energy would appear to be secondary, as generally speaking this factor affects all individuals to a similar degree and can be said to be dependent on senile changes in the lens to make its action effective. The nature of this senile change may be thought of as an hereditary idiopathic predisposition to early and progressive sclerosis. The hereditary nature of this exciting cause has probably not been noticed because of the scarcity of clinical examples or its assumed recessive nature. This factor may also act by disturbing the permeability of the lens capsule and as Friedenwald has suggested its decreased permeability in age would operate as a disturbing factor in the lens nutrition. This in turn upsetting the chemical metabolic balance, resulting in increased hydrolysis of the protein. That this is not the entire explanation is granted, in that the biological factors have not been considered, but until more knowledge has been acquired regarding these factors I feel justified in disregarding it. This nuclear variety then becomes a true senile cataract with senility acting as a primary factor in its etiology.

In considering the pathogenesis of senile cortical cataract, this condition may be thought of as the development of the cortical opacity. The pathology may be considered as one process. The coagulation of lens protein, produced under the influence of multiple and varied causes. This process begins by the influx of fluid producing subcapsular cracks, fissures and vacuoles, which become filled with an albuminous granular material. These appear as dark radiate sectors or club opacities at the peripheral of the lens. That this is the earliest change is disputed by some who believe the changes appear first in the deeper layers of the cortex as a nebulous opacity surrounding the adult nucleus. This and a similar confusion regarding the processes taking place in the future development, of cortical cataracts limits the value of any discussion concerning the causative factors. These variations in the pathological appearance may however be considered to arise as a variation in the nature, degree, or time of operation of the injurious factors. Accepting the subcapsular origin as being correct, further opacity formation in the deeper structures is generally agreed to take place by a process of swelling, and disintegration of the lens fibers, which later shrink end form a homogeneous mass, that is lighter, smaller, and darker than the normal lens. There are associated with these degenerative changes, proliferative changes in the lens capsule about which little is known. 62, 15.

With this rather indefinite picture of the processes taking place it is very difficult to assign any definite role to the causative factors concerned in the production of the cortical
cataract. In considering the role of the various factors producing senile opacity it may be of value to determine if possible which factors are primary, which are secondary or the result of primary injury, and which are merely coincidental or contributing factors.

Radiant energy in certain industries, glass blowing, metal working, etc., and perhaps in certain geographical areas, becomes a primary factor; but in the general walks of life its action may be considered to be only contributory to the various other factors concerned in the production of senile cataract.

That osmotic disturbances are at least secondary factors in the production of opacity is shown by the formation of the subcapsular water-clefts and the general swelling of the lens. Osmosis rises to a primary position in the true diabetic type of cataract, but in the common cortical variety it must assume a position secondary to permeability in the lens capsule before exerting its effect.

The biochemical changes are difficult to evaluate. The appearance of tyrosin, I believe, may be considered as merely a coincidental occurrence depending on the hydrolysis of protein. The disturbance of the auto-oxidative system cannot be dealt with so easily, but from observing the retention of the cystein reaction in traumatic and toxic cataract for considerable time after the opacity has been well established, I feel that in these cases at least that disturbances in this system are secondary or the result of primary injury to the lens causing coagulation, with the resulting decrease in the necessity for an oxidative metabolism. I see no reason for giving these chemical changes a more important role in the production of cortical cataract, unless under the conditions of the decreased permeability of the capsule in age, it becomes an active secondary factor producing opacity by not keeping the metabolism at a high enough level to sustain life, because of an insufficiency of nutrient material.

Of the local changes then, only an altered permeability of the capsule can be considered as a primary cause in the production of cortical opacity. To maintain this position its permeability is assumed to be decreased. The operation under this condition would be to increase the osmotic value of the lens due to the retention of the by-products of metabolism. This increased osmotic value would in turn cause an inflow in an effort to re-establish equilibrium. The effect of the decreased permeability on the internal metabolism of the lens to limit the supply of nutrient material and thus produce tissue death and the subsequent coagulation of protein. A decrease in the permeability of the capsule therefore becomes a primary local factor in the production of cortical opacity, but when considered with changes in the body as a whole it may become only a secondary influence.

In analyzing the changes of the body as a whole the senility, disturbed metabolism, and toxemia, all may be considered to be primary factors, or to become so under the influence of renal insufficiency.

Senility, if by this we mean the diseased condition of retrogressive metamorphosis, is capable of producing both metabolic and toxemic conditions, and conversely toxemia and disturbed metabolism are capable of producing senile changes.
Under these conditions no one factor can be said to reach a primary position as the causative factor in the formation of cortical opacity, but any one or all of them with or without the operation of the secondary factors of renal insufficiency and altered capsule permeability may be said to be the cause of cortical cataract.

Looking at this question a little less critically, in determining the relative frequency or likelihood of the operation of any of these general factors it seems rather significant that the age group afflicted with this disease is in a range between forty-five and seventy-five years, the average age being about sixty. It is also at this period of life when degenerative changes would be most likely to make their appearance.17. With this in mind, and admitting that altered metabolism, toxemia and local changes may by themselves play a major role in the production of opacity and that any of the secondary influences may alter the course of the operation of these factors, I feel that senility must still be considered the etiological factor in the pathogenesis of the more common of senile cataracts.

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