Since case records indicate that nitroglycerine and other vasodilators gave excellent results in the treatment of this condition, and, since untoward effects were absent, further trials with this method seem justified⁵.

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5. I am indebted to Dr. H. Alexander Brown, M.D., F.A.C.S., San Francisco, for his helpful co-operation and assistance in these tests; and to Drs. P. Lazoreve and L. Teile, Leningrad, for their articles on similar research.

CATARACTA BRUNESCENS—STUDY OF THE NATURE OF THE COLOURING SUBSTANCE

BY

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Clinical Considerations

CATARACTA Nigra (Wentzel, 1788) or more correctly named Cataracta Brunescens (Becker, 1881), because in the large majority of cases the lens presents only a more or less deep brown colour, is a rather unusual form of cataract. In our practice we have met it only four times among a total of 1,357 cases of cataract.

Some authors believe that it appears especially in myopic eyes, but only one of our four cases was short-sighted. Jess, Rollet Bussy considered that cataracta brunescens has a definitely worse prognosis than an ordinary cataract. They have frequently observed the appearance of iridocyclitis or of infections after the operation, perhaps due to the special predisposition produced by the high myopia. Our cases, just as those of Gifford and others, did not confirm this unfavourable prognosis. All four had a perfectly normal post-operative course.

Our observations can be summarised as follows:—*Case 1.* A peasant, aged 56 years, entered the clinic on October 19, 1925. The impairment of sight began a year previously in the left eye,

and six months later in the right. There had been no pain or inflammatory phenomena. On admission R.V.=counts fingers at 1 m. L.V. counts fingers at 0.60 cms. Skiascopic examination, which was possible in the R.E. only, showed a myopia of 7 D. The posterior polar cataract permitted the examination of the fundus, showing peripapillary choroidal atrophy. Intra-ocular pressure in both eyes 18 mm. Blood Wassermann negative. The left eye was operated on November 6, 1925. Extraction with iridectomy and capsulectomy. The lens was deep brown. Post-operative course normal. The sight remained, however, weak due to the numerous foci of choroidal atrophy.

Case 2. S. R., aged 62 years. Admitted June 28, 1932. The sight began to diminish in 1916. In 1918 she had her left eye operated on in another hospital. At the present time R.V. and L.V.=count fingers at 3.5 metres. The left eye presents a superior coloboma, the lens being subluxated externally in the inferior part. The pupillary reflex to light persists in the right eye. The light is perceived at 4.5 m. Intra-ocular pressure in both eyes=21 mm. Blood Wassermann negative. The right eye was operated on July 1, 1932. The lens extracted after iridectomy. Its great mobility made the capsulectomy impossible. We used the cystitome and the lens was extracted with Snellen's loop. It was very flat and deep brown in colour. Post-operative course normal. Vision, with +10 D. sph. amounted to 1/8.

Case 3. I. V., aged 58 years. Entered the clinic on August 6, 1932. R.E. operated on long ago. This eye with a correction of +10 D. sph. had vision of 1/2. Left vision had been diminishing for one year. The lens had become totally opaque. Light perception was still good. Intra-ocular pressure, both eyes=16 mm. Operation on August 19, 1932, with capsulectomy. The lens was brown with greyish peripheral masses. Post-operative course normal. Vision obtained with a correction of +10 D.=1/10.

Case 4. N. M., aged 52 years. Entered the clinic on July 6, 1935. The obscuration of the sight began in 1916, first in the right eye. For one year the patient saw nothing with this eye and only little with the left. On admission R.V. and L.V.=counts fingers at 20 cms. On slit-lamp examination one saw among the grey striations of the lens a brown colour extending through its whole thickness. Pupillary reflexes normal. Light perception for the right eye at 2.5 m. Intra-ocular pressure R.E.=18 mm., L.E.=21 mm. Blood Wassermann negative. General state good. Blood cholesterol 1.38 per cent. The right eye was operated on October 10, 1935. Extraction of the lens with iridectomy and capsulectomy. The lens was deep brown with thin greyish peripheral layers. The left eye was operated on October 16, 1935.

The lens presented the same aspect. No post-operative inflammation. On October 23 the pupil was occupied by a fine pigmentary net, so that no fundus details could be seen. Vision of the right with +10 D. correction=counts fingers at 1.5 metres. L.E.=1/10.

In summarising these four cases we note that the age of our patients was not too far advanced (52-62 years).

Our only post-operative complication was a secondary pigmentary cataract, which is generally rare, and has been observed especially in diabetic cataract. We must point out, however, that the vision has remained reduced. This affects somewhat the prognosis of cataracta brunescens, as compared with the usual senile cataract.

Chemical Study

Our last case gave us an opportunity of studying the chemistry of the colouring substance in cataracta brunescens. The problem still remains insufficiently elucidated. We find on one side authors who could not succeed in identifying any pigment at all. Mawas, Busacca, Magnasco, Carmi, Cirincione, Neuschuller, Speciale Cirincione believe that the colour is a simple physical phenomenon due to increased refractivity of the lens. The selective absorption of shorter wave-length radiations, should thus be simply determined by the progressive sclerosis of the crystalline fibres. The majority of the authors admit however the existence of a real colouring substance, accumulating slowly in the senescent lens.

Moauero could identify once in some cases pigment of blood origin. Everybody considers to-day that the presence of such pigments is merely accidental, and unrelated to the process which determines cataracta brunescens. In some of such cases, as happened in our last case, the lens extracted from the eye was stained superficially with a drop of blood. The water in which this lens was immediately washed gave the distinct spectrum of haemoglobin. But no haematic pigment could be identified in the substance of the lens.

The recent publications of Gifford and Puntenny and of Sauer-mann bring new arguments to confirm the older opinion of Elschmig, Zeinek, Sliussakow, Takeishi, Rollet, Bussy, Burdon Cooper, Gatti, Nicatti, and tend to prove that pigment of cataracta brunescens belongs to the group of melanin.

The chemical composition of melanin is not yet sufficiently known. It seems to represent a group of substances, structurally very closely related. Florence and Enselman characterise melanin as: "Black pigments whose apparition is bound to a transformation *in vivo* or *in vitro* of amino-acids principally of tyrosine."

Piettre, through acid hydrolysis, obtained from melanin small amounts of tyrosine, leucine and other non-crystallisable amino-acids. Alkaline hydrolysis seems to give more alanin. Piettre has found also sulphur and even fatty chains. The action of H_2O_2 can determine the production of small quantities of fatty acids.

Artificial synthetic melanins have been in fact obtained from tyrosine, through the action of special ferments, tyrosinases. Bloch has studied the transformation of a particular synthetic compound, the dioxyphenylalanin (dopa) under the action of a dopaoxydase, present in all places where melanogenesis takes place.

It seems, according to Rapper, that tyrosine or dopa suffer in their transformation into melanin, certain common modifications bringing to the formation of indolic rings. This correlates melanin with another amino-acid, which can result from the autolysis of proteins namely with tryptophane (acid amino-indolpropionic).

In what concerns the eye, the mechanism of production was announced by von Szily in 1911. Gatti thought to explain the brown colour of naphthalenic cataracts through an oxidation of tyrosine. Rollet, Bussy, Corrado and Nicatti have admitted the same origin for the pigment.

The condition for the production of melanin is thus the presence of two elements. A melanogenic substance of protein origin (tyrosine, dopa, perhaps tryptophane) and specific ferment tyrosinase or dopaoxydase. Whenever one of these two factors is present in a tissue we can identify it by adding the second one. The result will then be a production of melanin.

These reactions have been recently applied by Gifford and Puntenny and by Sauermann to the coloured lenses of cataracta brunescens. Gifford and Puntenny could not find any tyrosine in the lenses of cataract (senile, naphthalenic, or brunescens). Sauermann on the contrary found tyrosine and was able to detect also the presence of tryptophane in 65 per cent. of the cataractous lenses. The dopa method, which brings into evidence the oxidative melanogenic ferments, has given negative results in the cases of Sauermann and of Waelsh. Gifford and Puntenny have obtained, however, some clearly positive findings. They admit that the brown pigment is produced as a result of a slowly progressing autolysis of the lens proteins. The melanogenic amino-acids produced in the more external layers can diffuse and disappear from the lens. Only those resulting in the nuclear layers remain, and under the action of ferments similar to dopaoxydase, are transformed into pigment. Krause questions if the ultra-violet light should have also a rôle in this transformation of amino-acids into melanic substances. According to him even other amino-acids, leucin and cystine can produce melanin, whose composition is then so much more variable.

According to his own findings Sauermann thinks it is not necessary to admit the intervention of any dopaoxydase. Tryptophane is sufficiently unstable and labile to be transformed into a coloured substance without the action of such a ferment.

Burdon Cooper observes that ratio K/Ca which reaches in a normal lens 380/1 is in a cataracta brunescens 11/1 while in senile cataract only 1/1.5. He questions if K is not an activator of some melanogenic enzyme.

Previous authors studying the actual chemical behaviour of the coloured substance, had reached similar conclusions. Sliusakow thought to identify melanin through spectroscopic analysis, Takeishi through its decolouration by some characteristic bleaching agents (bromine water, chromic acid, K permanganate).

In fact the chemical identification of different pigments found in animal or vegetable bodies is quite difficult. Due to their complex and probably inconstant composition, their properties can hardly offer the possibility of classification. This has been attempted by some authors (Hueck, Vernes).

Our two brown lenses, extracted at a very short interval of days one after the other gave us an opportunity to apply these methods and to try a chemical identification of the colouring substance. One of the lenses was ground in a mortar with distilled water and the brown residue, dried, was utilised for some solubility reactions. The other lens was kept for microscopical analysis and was cut partly fresh or after fixation in formalin, and partly after paraffin embedding.

The following table gives the results of our analysis :

SOLUBILITY

KOH 3 per cent. warm	Soluble
KOH 3 and 10 per cent. cold	Insoluble
KOH 10 per cent. cold alcoholic	Insoluble
NO ₃ H 3 per cent.	Insoluble
C1H, CH ₃ COOH	Insoluble
C1H 3 per cent. alcoholic warm	Insoluble
SO ₄ H ₂ conc.	Insoluble. No colour
Water, alcohol, ether	Insoluble
Chloroform, petroleum ether	Insoluble
Xilol	Insoluble
CNK 1 and 10 per cent.	Insoluble

IRON REACTIONS

Prussian blue	Negative
Tirman Turnbull	Negative

DECOLORISING AGENTS

H ₂ O ₂ 3 per cent. and 10 per cent. ...	Negative
K permanganate 1/2000	Decoloured
Bromine water	Decoloured

BASIC DYES

Nilblue	Positive even after paraffin embedding
Neutral red	Intensely coloured before fixation and after paraffin embedding

OTHER REACTIONS

Sudan III	Negative
AgNO ₃ Fontana	Non reduced
Dopareaction 1/1000	Negative
Nitroprusside cystine reaction	Negative
Birefringent corpuscles	Absent

Our results confirm in the first place the existence of a real colouring substance in our lenses. As Schmorl observes, colour due to simple diffraction phenomena in connection with physical structure disappear when this structure is modified. In our case colour remained unmodified by drying, pulverising, treatment with xylol and paraffin embedding. It disappeared on the contrary under the action of the usual melanin bleaching agents, bromine water and K permanganate. But as Gifford points out, the best argument is its solubility in warm (sometimes cold) KOH solutions. We have succeeded in obtaining by means of boiling in 3 per cent. KOH, a yellow solution of the colouring substance. Such solutions have been obtained by Gifford, Elschmig, Zeinek.

The whole series of reactions leads us to admit that this substance belongs really to the group of melanic pigments. In fact, the absence of any colour reaction with concentrated H₂SO₄, the lack of solubility in lipoidic solvents, exclude a carotinoid, chromolipoid nature. The absence of iron excludes the presence of blood pigments (haemosiderin). The bleaching with K permanganate excludes also the possibility of haematoidin.

Absence of malaria, insolubility in strong acid solutions, absence of double refraction plead against the presence of malaria pigment.

On the contrary all the results seem in accord with the properties of melanic pigments, except the non-reduction of AgNO₃. Our

pigment could not be then a real typical melanin. It could however belong to the so-called lipofuscin or "Abnützungspigment."

Lipofuscin is found, according to Ashoff, especially in old individuals, as small yellowish to brown grains, accumulating in the cells, particularly in those of the muscles of the heart, intestines, seminal vesicles, in the epithelia of the seminal vesicles and of the pigmentary zone of the adrenal glands, testicles and other glands. In pathological conditions they are often numerous and appear especially in certain atrophic processes, giving a real macroscopic brown colour to these organs (brown atrophy of heart, liver or muscles). In the ganglial cells of the central nervous system, in the sympathetic or spinal ganglia, this pigment is found normally. It multiplies with age and in certain pathological processes can accumulate much sooner.

Recently Slatineanu, Nicolau, Balmus have found in a case of malarial coma, besides the malarial pigment, another pigment which they call "a product of metabolism" which we think belongs to the same group of substances.

Its chemical composition is not yet well-known. Salkowski thought it different from melanin. Bralen and Schmidtman on the contrary believed them related. Lubarsch considers them identical. Lipofuscin seems to be composed from a more or less constant lipoidic compound and from a melanic pigment. In opposition to melanin, it does not reduce AgNO_3 and accumulates just as the brown pigment of the lens slowly with the age.

According to Hueck another character which differentiates lipofuscin from melanin is its colourability in fresh, unfixed state, with 1 per cent. neutral-red solution. Lipofuscin is coloured by the basic dyes. It takes blue colour in a solution of nilblue even after treatment with lipoidic solvents, as in our case after paraffin embedding.

We must however add that even the normal lens substance has a special capacity to retain, and become stained by, histological dyes. Our normal controls were thus themselves coloured with neutral-red, so that the identification importance of this reaction is much diminished. We had the impression that the intensity with which the brown lens took, and especially retained, the dyes was distinctly greater. A section of ordinary senile cataractous lens embedded in the same block with our brown lens appears now slightly pink when the brown lens remains after one month still deeply red.

We should also mention that Kubik considered as related to lipofuscin the pigment of the Fleischer corneal ring, appearing during Wilson's hepatolenticular disease. Its real nature is just as much discussed as that of cataracta brunescens. This pigment differs however from our case through its easy solubility in KCN

Such differences could perhaps be due to real variations of composition. The inconstant presence of lipoids and perhaps of other atomic groups should give eventually different properties. The origin of lipofuscin should anyhow be (according to its name : Abnützung pigment) just as that of melanin, in the decomposition and transformation of proteins.

Cystein could bring the sulphur found in its molecule, tyrosine, eventually tryptophane should give the melanic colouring nucleus. We do not know if the ferments of the dopaoxidase type play any part in the genesis of lipofuscin.

In our case the dopareaction was negative. Even after 24 hours our sections, previously shortly fixed in formalin, presented only a homogeneous greyish tint, not different from that of the controls (ordinary senile cataract).

Bloch considers that while dopareaction and pigmentogenesis is present always in the epidermis, it takes place in the eye only in the embryonic stage or when a melanotic tumour appears. Winternitz found the tyrosine present in extracts of pig's uveal tissue. We believe that absence of tyrosine, and of tryptophane, thus of autolysis, and of the dopareaction, at the time of our research, does not exclude the possibility of melanogenesis according to the processes previously described. The long duration of time, in which the pigment accumulates only little by little proves that this process should not be intense or even continuous. As Gifford points out, the possibility of diffusion through the other layers of the lens and through its capsule, explain in part why we cannot find constantly the elements we look for.

With this we reach the last point of our discussion. All usual pigments (lipofuscin included) are found in cells in the form of grains, well individualised. In the lens of brown cataract, in our case, and in the cases of other authors (Búsacca) the colour seems uniformly distributed, staining homogeneously all the fibres. Such homogeneous colouration is signalised also in the case of chloroma, where green pigment, of a nature as yet unknown, stains uniformly the cells of the tumour. This fact has not yet been pointed out in the case of melanin or lipofuscin. We must not forget however the special nature of the lens fibres. The protoplasm of cells having an active life and a complex organisation tend to isolate any foreign substance such as the pigments which accumulate and load it. It individualises them as pigmentary grains. On the contrary the fibres of the lens, through their function must assume the most homogeneous structure, and distribution of substances, in relation to the function of refraction and transparency. When treated with neutral-red it takes also a homogeneous colouration.

On the other hand, some pigmentary grains have been signalised

by some authors in cataracta brunescens. Takeishi described real grains, decolourised by oxydising agents. He considered them to be melanin grains. Gifford finds that the dopareaction shows some granulations intensely coloured in black.

It seems that the colouring substance accumulates slowly during life and diffuses homogeneously through the crystalline fibres. At the beginning they remain localised only in the nucleus and then in more rare cases occupy all the substance of the lens. As Becker has stated long since and as Vogt and Gifford pointed out again, it is very probable that between the ordinary senile yellow nucleus and cataracta brunescens, is a real transition representing the stages of the progressing processes.

Conclusions

Typical cataracta brunescens is in our practice a rare form of cataract (four cases from a total of 1,357).

Its removal presented no particular difficulties and the post-operative course was normal and devoid of any inflammatory complications. The vision has remained low, rendering therefore the prognosis somewhat inferior to that of ordinary senile cataract.

Two lenses from the same patient were chemically investigated.

A coloured substance could be extracted with hot KOH 3 per cent. All the chemical tests made, tend to prove that this substance belongs to the so-called "Abnützungspigment" (lipofuscin).

The pigment accumulating normally with age in certain muscular, glandular or nervous cells, can sometimes appear earlier in certain pathological conditions. It seems closely related to melanin and possibly could be produced in the same way by transformation of autolytic products of proteins.

In our case the dopareaction was negative. This does not exclude however the possibility of an intermittent intervention of certain oxidative, pigmentogenic enzymes as is advanced recently by Gifford and Puntenny.

Cataracta brunescens represents probably a far advanced stage of the process which produces usually yellow senile sclerosis of the lens. As in the brown atrophy of heart and of muscles it represents the same process of accumulation of a pigment belonging to the group of lipofuscin.

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“POSTERIOR NEEDLING” IN THE TREATMENT OF LAMELLAR AND OTHER FORMS OF SOFT CATARACT

BY

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GLASGOW

IF one may judge by the absence of all reference to it in current text books, the method of causing solution and absorption of the crystalline lens, by division of its posterior capsule, must be quite unfamiliar to at least the younger ophthalmic surgeons of the present day. I learned the operation from my seniors, and it has been practised in Glasgow for many years, both in the Eye Infirmary and in the Ophthalmic Institution, but I have been unable to trace its source.