for the latter to find employment near home, many of them walking or bicycling to work and returning home to their midday meal. Many of the office workers, on the other hand, had long journeys at the rush hours in conditions which must tend both to lower resistance and to facilitate the spread of any infection. An interesting statement concerning this subject was published in a recent report of the Industrial Health Research Board:² in clerical trades and light industries it was found that the factory worker had a lower rate of sickness than the clerical worker.

Conclusions

1. Contact with pulmonary tuberculosis is an important factor in the aetiology of pulmonary tuberculosis in young adults, and therefore it should be possible to detect the disease in its early stage in many instances by examination of all those with a history of such contact.

2. About four out of every five of young adults suffering from pulmonary tuberculosis who have been in contact with a known case of infection develop the disease within five years of exposure to the last known contact with infection—a fact which stresses the value of continuing the observation of contacts for at least five years after they were known to be last exposed to infection.

3. There is a history of household infection in 82 per cent. of the contact cases.

4. History of exposure to tuberculous fathers is almost twice as frequent as history of exposure to tuberculous mothers.

5. In about half of the contact cases spread of infection is not obviously due to transmission of the disease from parent to offspring, but in many cases infection is apparently introduced into the household by a brother or sister.

6. It is important to realize that 60 per cent. of the young adults who develop pulmonary tuberculosis are unaware of any contact with the infection.

7. In non-contact cases the toxæmic type of onset is more common than the non-toxæmic (70 per cent. *versus* 28 per cent.). If all classes of contact cases are taken together the toxæmic and non-toxæmic types of onset occur in about equal proportions. It appears, however, that if there is an interval of over five years between the last known exposure to infection and the onset of the disease the onset is more likely to be of the non-toxæmic type.

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R. Liberti (*Il Policlinico*, Sez. Med., August 1st, 1936, p. 400) states that the mortality among 143 cases of tetanus admitted to the Clinic for Infectious Diseases of the University of Rome from 1922 to 1935 inclusive ranged annually from 22 to 83 per cent., the average being 51 per cent. All the cases were treated by anti-tetanic serum administered by various routes, combined with bromide and chloral or morphine. Dufour's method of deep anaesthesia by ether or chloroform for at least half an hour, and repeated, was used in twenty-eight cases with a mortality of 50 per cent., which was higher than that of cases not so treated, while 35.6 per cent. died of bronchopneumonia as compared with only 1.8 per cent. of those not so treated. In conclusion, Liberti states that Cole's method of continuous avertin anaesthesia for several days deserves consideration.

RECENT OBSERVATIONS ON THE BIOCHEMISTRY OF THE LENS*

BY

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For this paper I have reviewed the work of the past three years in order to give an account of the more important observations on the biochemistry of the lens. Recently the search for the cause of cataract has been in three main directions:

1. The discovery of new methods of producing experimental cataract.
2. The investigation of general metabolic changes which may be associated with cataract.
3. The identification of new substances in the lens.

The results of these biochemical experiments are more closely related to clinical facts than they have been heretofore. For instance, among the new methods employed for producing experimental cataract are:

1. A disturbance of carbohydrate metabolism.
2. A deficiency of vitamins.
3. Investigation of hereditary cataract in animals.
4. The administration of toxic substances.

The first of these—that is, a disturbance of carbohydrate metabolism—is directly related to the clinical problem of diabetic cataract. The rapid changes in refraction which can accompany a rise or fall of blood sugar in the diabetic patient are well known, and it is generally accepted that the development of cataract in a young diabetic is a bad prognostic sign. It is interesting to note that Chaikoff and Lachmann (1933) found lens changes in eight out of ten dogs which had been made diabetic by the removal of the pancreas, and had been kept in good health for periods up to two years by the administration of insulin. The lens opacities varied from peripheral striations to diffuse irregular opacities resembling early senile cataract. The development of cataract bore no relation to the duration of the diabetes nor to the age of the dog. The animals were receiving a full protein and vitamin diet.

Carbohydrates and Cataract

Mitchell and Dodge (1935) accidentally observed mature cataract in three rats which were on a diet containing 70 per cent. lactose, and proceeded to a full investigation of the effects of a high carbohydrate intake. All of the rats given this diet showed lens changes, which in about half of them developed into mature cataract in some ten weeks. The addition of calcium gluconate had no appreciable effect. With lower percentages of lactose the cataract developed more slowly and fewer became mature. Rats subjected to the diet at an early age—that is, under 30 days old, were more susceptible than older rats. Diets containing 70 per cent. of starch, dextrin, or maltose, or 50 per cent. of sucrose or maltose, had no effect on the lens. The lens opacities appeared either as a zone of defraction round the nucleus, followed by nuclear opacity, or began as flake-like opacities in the anterior cortex. It is interesting to find that there was an increase of calcium content in the eyes which developed cataract, but no corresponding changes in the calcium content of the blood or bones.

Lactose has some association with calcium metabolism, and it is said to aid the absorption of calcium from the intestine (Bergeim, 1926) and to have a favourable effect on the calcification of rachitic bones, so that it is quite possible that this sugar has some effect on the permeability

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of the lens capsule. Rats on lactose excreted in the urine a large amount of sugar which appeared to be galactose, a simple sugar which can be obtained from lactose by hydrolysis.

Rats are known to absorb galactose more rapidly than other sugars (McCance and Madders), and there is some evidence that galactose has a more marked effect on the lens than lactose. Mitchell (1935) found that rats fed on a diet containing 35 per cent. galactose developed mature cataract very rapidly—actually in about nineteen days; they also showed marked galactosuria and an increase of calcium in the eyes. Yudkin and Arnold (1935) have performed similar experiments on albino rabbits and obtained results confirming those of Mitchell and Dodge. With 70 per cent. dextrose the lenses were clear and the blood calcium was normal, while the latter was slightly raised on a galactose or lactose diet. They found that on galactose young animals formed nuclear cataracts, whilst older animals developed cortical cataracts. They suggest that galactose may have a direct toxic effect on the growing parts of the lens, or that it may affect it indirectly by upsetting the calcium metabolism of the body.

The use of such high percentages of sugar to produce cataract is certainly open to criticism, but one must remember the high level often reached by the blood sugar in diabetes. The interesting effects of lactose make one wonder whether this sugar plays any part in the development of lamellar cataract, since it is normally present in the circulation during the latter part of pregnancy, and we know that the lens changes in lamellar cataract are laid down in embryonic life.

Effects of Vitamin Deficiency

If we now turn to the effects of vitamin deficiency we must remember that in the past few years the vitamins have increased in number and complexity. They are no longer the three simple substances A, B, and C. Vitamin A has a direct connexion with night-blindness. B is subdivided into several factors, of which B₂ (or G) and lactoflavin are of importance in the investigation of cataract, while vitamin C has been identified with ascorbic or cevitamic acid (Szent György), and has been found to be present in the lens in amounts varying with its pathological condition. It is well known that a deficiency of either A or G will produce a keratitis.

In the experimental production of cataract there are only a few instances of obtaining it as a result of a deficiency of vitamin A. Blackberg and Knapp (1934) said that puppies on a rachitogenic diet developed not only dental caries and conical cornea (a combination of symptoms found to occur clinically), but that on a later date the sutures of the lens became very marked, and discrete opacities appeared which finally developed into mature cataract after six months. They ascribe these changes to disturbance of the calcium-phosphorus balance brought about by the lack of vitamins. V. Szily and Eckstein found zonular cataract in the young of rats deprived of vitamin A, but Stepp and Friedenwald have failed to confirm this.

The effect of vitamin B₂ or G deficiency has been the subject of a large number of experiments. Langston and Day (1931 and 1934) in America have reported an incidence of 100 per cent. cataracts, which matured in an average of seventy-two days, both in albino rabbits and in rats deprived of vitamin B₂. They found that the appearance of cataract was delayed where small but insufficient amounts of B₂ were added, and this could be correlated with the rate of growth. Their results were so consistent that they concluded that the development of cataract might be used as a better criterion of vitamin B₂ deficiency than the one usually employed—namely,

the appearance of dermatitis. Day, Langston, and Cosgrove also produced cataract in mice, chickens, and monkeys by the same means.

In contrast to these results O'Brien (1932) and Yudkin (1933) report that cataracts only occur in rats deprived of vitamin B₂ at an early age and not in older animals, while in this country Bourne and Pyke (1935) carefully repeated the work of Langston and Day and obtained an incidence of cataract of only 31 per cent., whereas dermatitis appeared in almost every case. Other observers—for example, Daniel and Munsell (1933) and Ray, György, and Harris (1935)—have also kept large numbers of rats for a long time on a B₂-deficient diet without any cataract developing. Nevertheless Bourne and Pyke are of the opinion that some dietetic factor may be concerned, and that the recent work of separation of vitamin B₂ into flavine and a subsidiary substance should facilitate the solution of the problem. In fact, Fischer (1935) has stated that flavine is present in the lens. Bourne and Pyke (1935) made one other interesting observation: that no cases of cataract occurred in a small number of rats receiving a diet deficient in B₂ but to which there had been added 1 per cent. cystine, a substance which normally abounds in the lens but which is absent in cataract.

We associate lack of vitamin C with the production of scurvy, and Monjukowa and Fradkin (1934) appear to be almost the only observers who have found any lens changes associated with the lack of this vitamin. They reported six cases of clouding of the lens out of twenty-five scorbutic guinea-pigs, and stated that puncture of the anterior chamber led to a rapid development of cataract, whereas in normal animals this did not appear. Further, lens opacities occurred on the second day after birth in young guinea-pigs whose mothers had been deprived of vitamin C during pregnancy. Bellows (1936) failed to observe lens changes in guinea-pigs which had been kept for two months on a vitamin C deficient diet, while Bietti (1936) found in guinea-pigs slight lens changes which were more marked if the diet was poor in cystine as well as in vitamin C. Vitamin C actually bears a more interesting relation to the metabolic processes of the normal lens, to which I will refer again later.

Hereditary Cataract

It is generally agreed that in all experimental work where stock animals—such as, rats—are used one has to guard against the appearance of hereditary defects. This is particularly the case where attempts have been made to produce cataract in young animals by the injection of lens extracts, or lens proteins, into the parent animal. Rabbits have been used more than any other animals, and they are specially prone to show hereditary defects of the eyes.

Noted observers—such as, Nettleship (1909), Bishop Harman (1910), Norman Bennett (1901), and Hornback (1932)—who have reviewed the subject of hereditary cataract, have pointed out that in man these cataracts are related to disorders such as deficient calcification and dentition, and muscular atrophies or dystrophies. Hornback's contribution to our knowledge is of special importance, since he has stressed the fact that hereditary cataract in man appears apparently as a dominant character, but with occasional lapses that are difficult to explain. It is transmitted in a way that can be explained, however, on the assumption that it is the *predisposition* to cataract which is transmitted as a true dominant character. Whether or not cataract itself develops depends upon the association of this predisposition with some other factor. A nutritional or endocrine disturbance may obviously constitute this other factor.

It is highly probable that the same is true in animals. V. Hippel has published an interesting account of a dominant hereditary cataract in dogs in which the lens changes began in embryonic life, while recently Bourne, Pyke, and I have been able to test the inheritance of cataract in rats. By the courtesy of Messrs. Bemax we acquired from their stock colony two adult rats which were normal, except that each had bilateral mature cataract. From them we have bred four generations of rats. The cataract appears to be inherited as a recessive character. It first begins to appear about two months after birth, and is associated with certain degenerative changes in the retina. We hope at a later date to give an account of its genetics and its histological and ophthalmological appearances. It certainly provides an excellent opportunity for testing the theory that the appearance of hereditary cataract is conditioned by nutritional disturbances.

Effect of Toxic Substances

We now come to the last of the methods of producing cataract—the administration of toxic substances. The effects of naphthalene and dinitrophenol are outstanding. The latter drug has recently been employed in America as a popular remedy for slimming, and since July, 1935, there have been a hundred or more cases recorded in which patients have suffered from marked deterioration of vision, beginning perhaps several months or even a year after they had ceased to take the drug. The loss of sight was found to be due to changes in the lens, which began as "brass-filing" or snow-flake opacities (Veasey, 1936) and within a few weeks rapidly developed into cataract. Spaeth (1936) describes a case in which complete liquefaction of the cortex occurred, and the lens was reduced to a number of particles floating in a milky fluid inside the lens capsule. This devastating effect may be due to the fact that dinitrophenol is said to cause a tremendous increase in tissue oxidation. In a review of twenty cases Cogan (1935) was unable to find any relation to the total amount or time of taking the drug, or to the loss of weight it produced. Most of the patients were young, the average age being 37, and some were taking only small doses under the care of a physician. Both Cogan and Spaeth have reported cases which showed symptoms resembling those of a parathyroid tetany, and Spaeth administered parathyroid extract with calcium lactate with benefit. Apparently the lens was the only part of the eye affected, as removal of the cataract restored the vision.

The work which I described a few years ago on the effect of naphthalene on the lenses of rabbits seemed academic, but it has suddenly acquired a clinical interest, in the light of these reported cases of dinitrophenol cataract, since the two substances are closely related chemically. It was generally believed that an aromatic hydrocarbon such as naphthalene could not be metabolized by the body, but Bourne and Young (1934) have made a discovery of great importance in showing that in rabbits naphthalene is conjugated with cystine and is excreted as 1- α -naphthyl-mercapturic acid. They not only isolated this substance from the urine of the rabbits, but were also able to synthesize the pure substance.

Such authentic chemical evidence is always of value, and since naphthalene causes cataract, and the lens is particularly rich in cystine-containing substances, such as β -crystallin and glutathione, it is tempting to adopt Bourne and Young's suggestion that the cataract caused by naphthalene may be due to the depletion of the lens of its store of cystine. In fact, Tsuji (1932) has shown that a naphthalene cataractous lens will no longer give a positive reaction for cystine.

Metabolic Changes in Cataract

With regard to the investigation of metabolic changes which may be associated with cataract in man, the ordinary constituents of the blood, cholesterol salts, sugar, and so on, have been estimated repeatedly without any significant difference being found in patients with cataract, although there is some slight evidence that the blood calcium may vary, particularly in endocrine cataract (Alajmo and Rubino, 1935). Very little is known, however, of sulphur metabolism, or of the relation it bears to the substances glutathione and cystine, either in the normal subject or in those with cataract.

As a preliminary investigation last year (Campbell, 1935) I estimated the glutathione in the blood of patients with senile cataract and in those with other ocular conditions, and found that there was no marked variation in the reduced glutathione content of the blood. It was also apparent that age and diet had no effect, even when the amount of sulphur ingested was varied from maximum to minimum by the use of high and low protein diets of the same calorie value. The oxidized glutathione of the blood was more variable but showed no significant change (Campbell, 1936).

Bourne and I also investigated the sulphur metabolism in a number of patients, and were unable to show any abnormality in those suffering from cataract. The investigation was a tedious one, as it involved numerous fractional analyses of the urinary sulphur and keeping the patients on controlled diets for several days. There was no indication of an increased output of neutral sulphur such as might be expected if cystine were being lost from the body, nor of any active detoxication as shown by the excretion of ethereal sulphates. The cataractous patients seemed to have as good a sulphur metabolism as the normal controls (Bourne and Campbell, 1936). Of course there may be some abnormality present which is not revealed by the methods of analysis now in use.

Bellows (1936) has investigated the vitamin C in the blood and has found that it is normally present in the amount of 1 to 2 mg. per 100 c.cm., whereas in cataractous patients it is slightly less. He also determined the response to an intake of vitamin C by giving 150 c.cm. of orange juice and estimating the vitamin C content of the blood immediately before and thirty minutes after the administration. This dose had almost no effect in the cataractous patients, but caused a slight increase in the normal; the vitamin C in the blood of cataractous patients could be raised after large doses had been taken for several days. In support of the theory that a vitamin C deficiency may exist, Harris and Ray (1935) have shown that, judging by the urinary output of vitamin C, a subclinical type of scurvy is not uncommon in adults, and this is, of course, more likely to occur among the poorer classes, in whom cataract has a higher incidence.

Chemical Reactions in the Lens

This leads us to a consideration of the lens itself, for it has been demonstrated recently by many observers that its reducing property is not wholly due to glutathione, as was supposed, but is due also to vitamin C, of which it contains a relatively large amount. According to Muller and Buschke the lens contains 30 mg., while the aqueous humour contains about 12 mg. per cent. of vitamin C, as contrasted with the blood and cerebro-spinal fluid, which contain only a small amount (1 to 2 mg.). Vitamin C, like glutathione, disappears from the cataractous lens (Euler and Malmberg, 1935), while with age it decreases in the lens and increases in the aqueous (Muller and Buschke, 1934). There is less vitamin C in the aqueous humour of the aphakic eye than in the normal (Bellows, 1936).

Muller, Buschke, and Fischer (1934) are of the opinion that vitamin C provides the metabolic link between the oxidation and reduction system of the lens, and the media outside the lens. From their experiments they suggest that the following reversible reaction takes place and would constitute a cycle of respiration.

Probably vitamin C can travel between the lens and aqueous, whereas the glutathione is retained in the lens. Szent György has shown that vitamin C will rapidly oxidize reduced glutathione, while there is some evidence that vitamin C can be derived from the reduction of sugar by glutathione. That there is some such balance between lens and aqueous humour is shown by the fact that when the lens and aqueous are incubated together the lens shows a slight gain, the aqueous a slight loss of vitamin C, whereas when incubated alone the aqueous shows a considerable loss.

AVERAGE OF TEN EXPERIMENTS
Percentage Weights of Vitamin C

Lens		Aqueous Humour		
Fresh	Exposed 5 hours to Aqueous Humour under Paraffin	Fresh	5 hours with Incubated Lens	5 hours Incubated alone
47.7 mg. %	50.5	20.8	16.1	8.3

Muller has shown that the ability of the lens to prevent oxidation of the ascorbic acid of the aqueous humour is soon lost in rabbits that have been fed with naphthalene. It is interesting to note that vitamin C is held back tenaciously by the lens, even in an animal dying of scurvy (Ray, György and Harris), although the vitamin C content of lens and aqueous in different animals bears no relation to the sensitiveness of the animal to a lack of vitamin C (Muller and Buschke, 1935).

In addition to the discovery of vitamin C, Fischer (1935) reports that minute quantities of fluorescent substances are present in the lens. The normal lens contains flavine, which he identifies with lactoflavine of vitamin B₂, and which appears to be replaced in the cataractous lens by a substance corresponding to lumiflavine, a photolytic product of flavine. The other substance is probably dimethylalloxazine. It fluoresces blue, is present in both normal and cataractous lenses, and increases in amount with age. György (1935) could find no biologically active lactoflavine in the lens, but this might be explained by the fact that lactoflavine is easily destroyed by ordinary daylight.

Conclusion

In conclusion, a review of this kind is necessarily disjointed, but I cannot help feeling that definite progress is being made towards a solution of the problem of cataract. Certainly the biochemical work of recent years has been more consecutive—there has been closer association between the different investigators, and greater attention has been paid to the clinical side of the problem.

An excess of sugar or deficiency of vitamin, a disturbance of calcium metabolism or loss of cystine from the lens, are all very likely factors in the causation of cataract, and even the effects of rare toxic substances have acquired an unexpected significance. Not only new facts, but those with which we are already familiar, are assuming a more orderly arrangement.

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S. Lomholt (*Ugeskrift for Laeger*, August 27th, 1936, p. 799), who is in charge of the skin department of the Finsen Institute in Copenhagen, gives an account of a search conducted by himself and a colleague in March, 1936, for warts and interdigital fungi (epidermophytia interdigitalis) among the school children of Copenhagen. As far as the feet were concerned, they found that warts were common in all the classes examined, the incidence of such warts being about 6 per cent. among the girls and only 3.8 per cent. among the boys. On the other hand, boys were much more subject than girls to warts on the hands, presumably because boys are more grubby than girls and scratch themselves oftener, and thus pave the way to an infection. No relation could be established between the warts on the hands and on the feet, and it was most exceptional for the same scholar to grow warts on both his hands and his feet. This is the more surprising as the infecting agent is presumably one and the same. Warts on the hands afflicted three times as many children as warts on the feet. In a class of boys from exceptionally poor homes warts on the hands were found in 23 per cent. The treatment mentioned by the author for warts on the hands includes suggestion, electrolysis, electrocauterization, electrocoagulation, radium, scraping, and patience, most warts disappearing of themselves if given time. With regard to the incidence of warts on the feet, which the author considers as a typical school infection, he notes that there has been an appreciable decline since 1934, and this may be traced to the prophylactic measures introduced in school lavatories and baths with the object of discouraging foot-to-foot infections. When the floors of such quarters are amenable to frequent washing and disinfection, without being made dangerously slippery, much can be done to prevent infection. While such measures promptly reduce the incidence of warts, interdigital fungi are much more refractory to them. Once such fungi are safely lodged in the skin of toes kept in close contact with each other by tight footwear it is very difficult to get rid of them.