THE EYE AND CYSTIC FIBROSIS OF THE PANCREAS: A RÉSUMÉ*

BY *Gordon M. Bruce,* M.D.

FOR ABOUT SIX YEARS the eye findings encountered in cases of cystic fibrosis of the pancreas have been under joint study at the Babies' Hospital and the Institute of Ophthalmology in New York. The purpose of this paper is to present with the minimum of detail a summary of the work done in the past and to comment upon the present situation.

Cystic fibrosis of the pancreas, or mucoviscidosis, is a congenital familial disease of children and young adults. It is characterized by malnutrition, steatorrhea, chronic cough, bronchopneumonia, emphysema, distended abdomen, muscular wasting, and cyanosis. The laboratory findings include elevated concentration of sodium chloride in the sweat, diminution of trypsin in the duodenal fluid, elevation of blood CO_2, and X-ray evidence of bronchopneumonia and microcardia. Half of the patients die before the age of 10 years and 80 per cent before the age of 20.

In 1958 we[1] were asked to examine the eyes of two brothers suffering from cystic fibrosis of the pancreas and complaining of poor vision. They showed papilledema, tortuosity of the veins, hemorrhages, and, in the case of one brother, a cyst in the macula (Figures 1 and 2). Since then we have examined the eyes of more than 200 patients with this disease. In some cases we obtained drawings of the fundi (Figures 3 and 4), in others photographs (Figure 5), in others pathologic sections (Figures 6–11). Sometimes we obtained combinations of these in the same individual (Figures 12–14).

It shortly became evident that the type of retinopathy observed in the first two patients occurred in other sufferers from cystic fibrosis with a regularity that could not be ignored. We thereupon set out to discover the immediate cause. We first investigated the systemic venous pressure. It was found that high venous pressure could exist without

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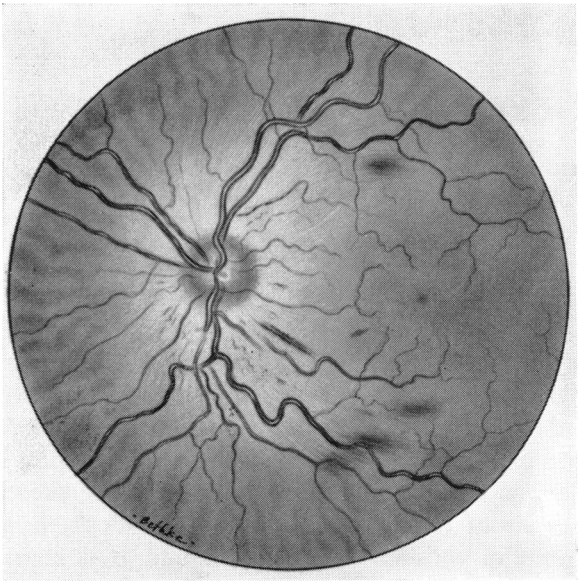


FIGURE 1. FUNDUS DRAWING. PAPILLEDEMA, TORTUOUS VEINS, HEMORRHAGES.

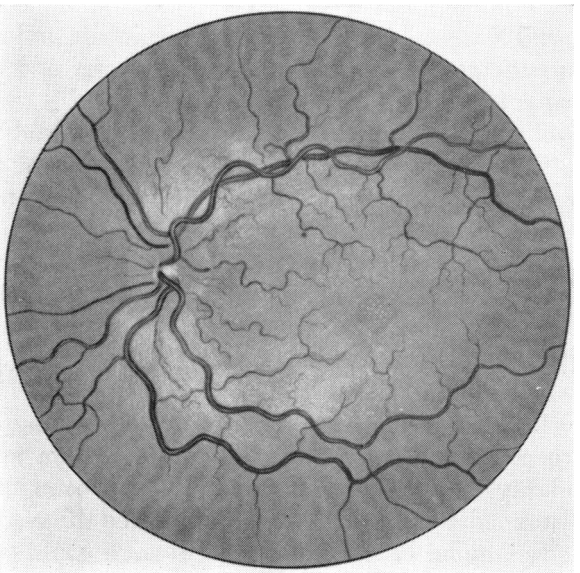


FIGURE 2. FUNDUS DRAWING. PAPILLEDEMA, TORTUOUS VEINS, CYST AT MACULA.

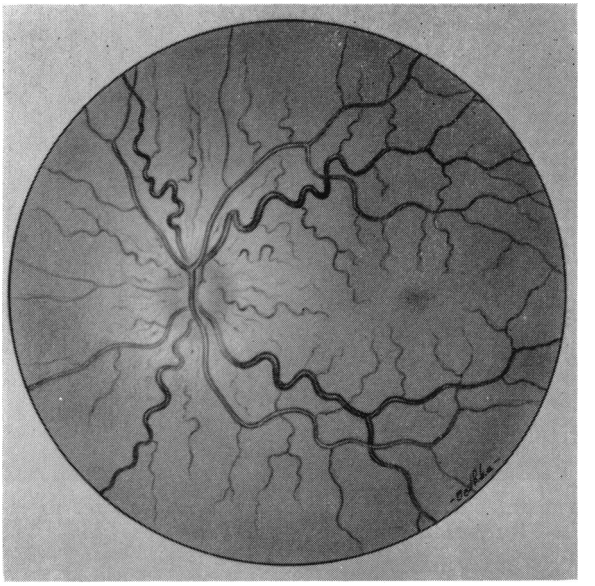


FIGURE 3. FUNDUS DRAWING. PAPILLEDEMA, TORTUOUS VEINS, OCCASIONAL SMALL HEMORRHAGES.

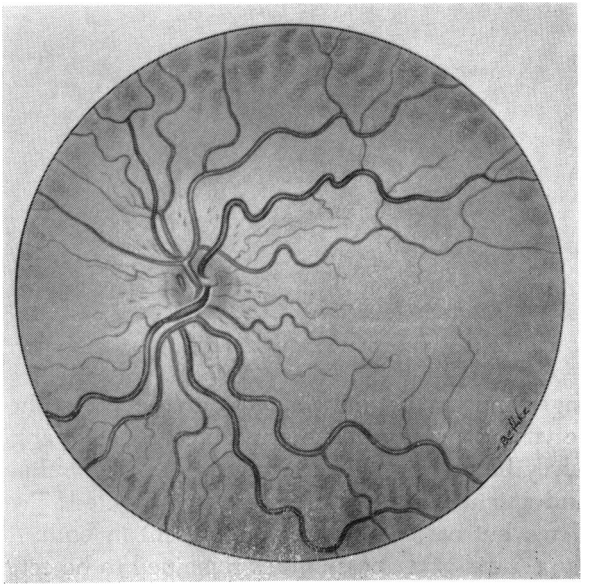


FIGURE 4. FUNDUS DRAWING. PAPILLEDEMA, TORTUOUS VEINS, HEMORRHAGES.

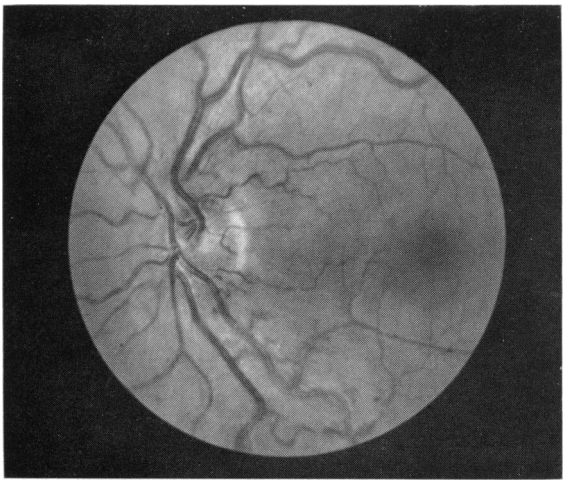


FIGURE 5. FUNDUS PHOTOGRAPHIC KODACHROME. PAPILLEDEMA, TORTUOUS VESSELS, HEMORRHAGES.

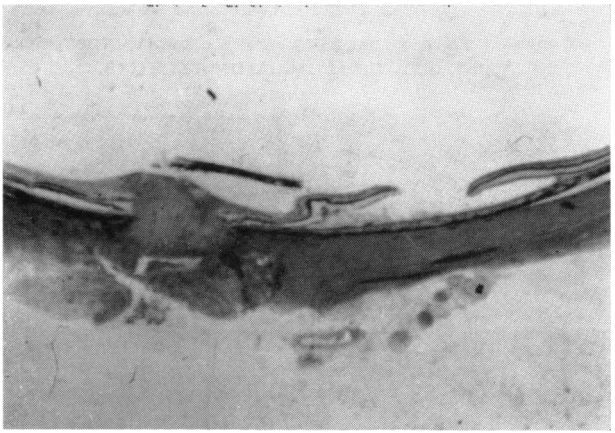


FIGURE 6. PATHOLOGY SPECIMEN. HOLE IN MACULA.

retinal changes and that retinal changes could occur without derangement of the venous pressure. The same inconsonance appeared when anemia, polycythemia, right heart failure, hyperglobulinemia, serum viscosity, and spinal fluid pressure were investigated. Two cases had cerebral edema but cardiac failure was present in both.[2]

Obviously, certain other possibilities remained to be considered. For example, all of the patients had been given large and repeated doses of chloramphenicol. It had long been established[4–7] that this drug

could produce pathologic changes in the optic nerve. Here again there were discrepancies, but we thought that in at least four cases we were dealing with retrobulbar neuritis. One youngster who had been receiving chloramphenicol in the usual amount of 50 mg./Kg./day suddenly developed central scotomas. His fundi were not remarkable at this time, but he subsequently developed optic atrophy. Another patient lost vision with dramatic suddenness. The visual acuity improved from 4/200 to 20/25 when the antibiotic was discontinued, but her general health deteriorated so much that therapy had to be resumed. Fortunately, she underwent no visual regression, but her discs were thought to be somewhat pale. Just before her death, a

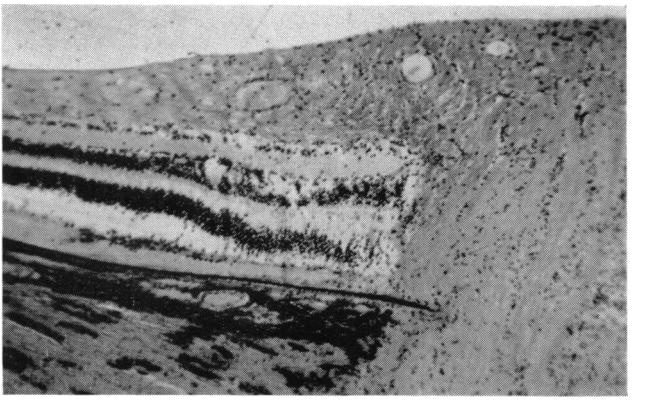


FIGURE 7. PAPILLEDEMA.

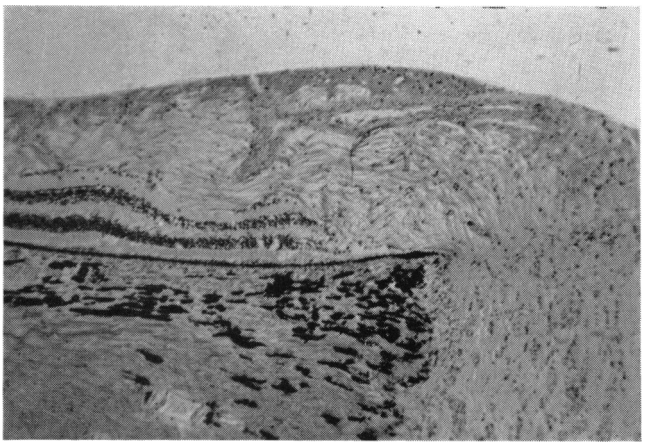


FIGURE 8. PATHOLOGY SECTION × 100. EDEMA OF DISC.

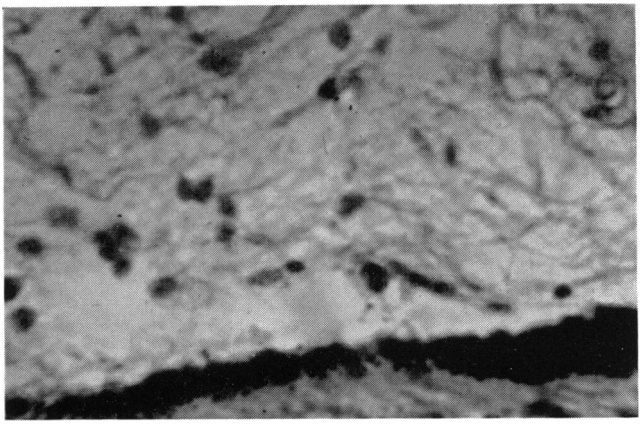


FIGURE 9. EDEMA OF DISC O.S. × 430.

year or so later, her visual acuity was 20/20 in each eye. The ophthalmic pathology report was essentially negative.

The other two cases were similar in history and course.

Inasmuch as arteriolized blood pH, pCO_2, and serum electrolytes were normal in three of the above cases available for such studies, we believed that a toxic factor was responsible for these symptoms, and that chloramphenicol was the most likely cause. Since many other patients had received large doses of the antibiotic without developing retrobulbar neuritis, we postulated that an additional factor, such as idiosyncrasy to the drug, must be necessary for the production of this clinical picture.[8]

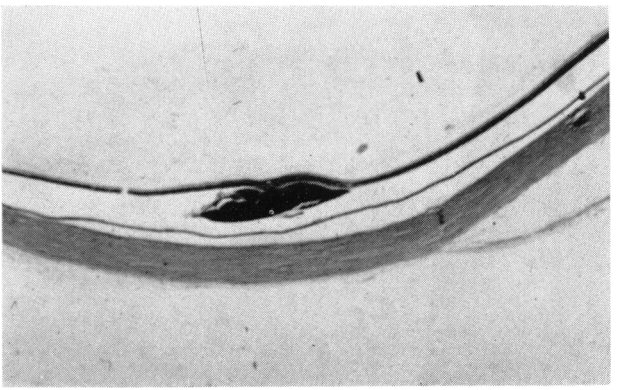


FIGURE 10. PATHOLOGY SPECIMEN. RETINAL HEMORRHAGE.

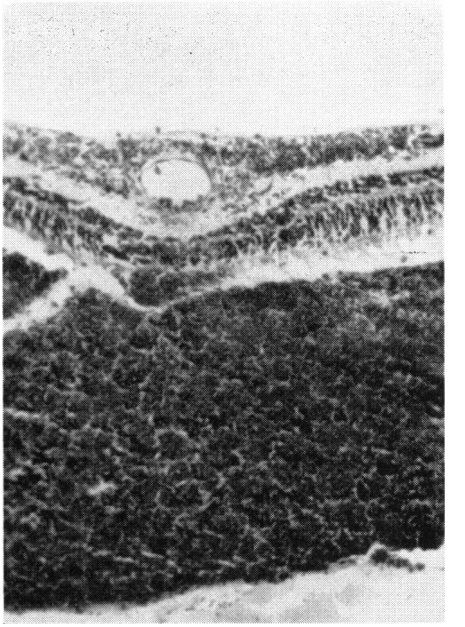
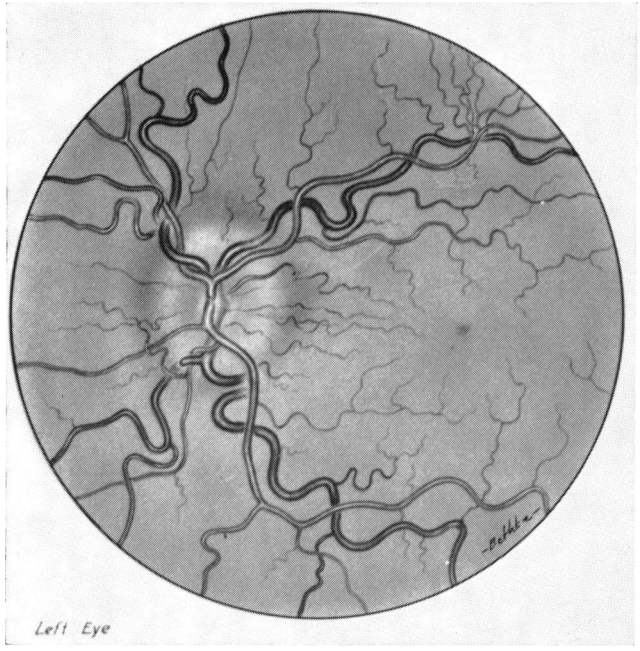


FIGURE 11. RETINAL HEMORRHAGE.

It was now evident that the search for the contributing factor had hitherto been fruitless, and we returned to an aspect of the problem that had puzzled us from the first. We knew that an increase in blood CO_2 had been accompanied, in other pulmonary diseases, by papilledema and tortuosity of retinal veins.[9–14] We were surprised that in only two out of the first 24 patients with these ocular signs had the CO_2 been elevated. We thereupon decided to abandon the somewhat inexact older methods, and to determine the CO_2 content in arteriolized blood by the Astrup technique. Increased levels began to appear, even when previously negative blood was examined. The pattern that emerged was a definite correlation between the concentration of CO_2 in the blood and the amount of papilledema and venous tortuosity.

We then decided to search the wards of the Presbyterian Hospital for patients with long-standing pulmonary insufficiency. We found two patients with chronic pulmonary emphysema, two with kyphoscoliotic pulmonary disease, and one with the so-called "Pickwickian" syndrome or hypoventilation associated with obesity. All had CO_2 retention, four had papilledema, venous tortuosity, and macular edema,



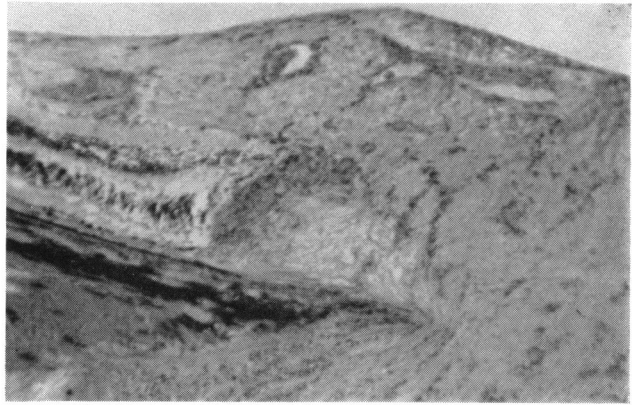


FIGURE 12

Fundus drawing showing papilledema. Pathology section showing papilledema, same eye.

and one had normal fundi. All had blurred discs and increased tortuosity of retinal veins.

We next studied the effect upon the retinal vessels of artificially produced hypercapnia. In collaboration with the Departments of Physiology and Anesthesiology at Columbia, Spalter[15] set up an ingenious experiment whereby he was able to produce in the dog the hypercapnia found in cystic fibrosis patients. By ophthalmoscopy, photography, and actual angiometry he was able to prove that the dilatation and tortuosity of the retinal veins could be controlled by varying the constant of CO_2.

COMMENT

This investigation was beset from the first by the variants of interpretation inherent in all medical disciplines. The patients, young, ill, often gasping with air-hunger, afforded little opportunity for detailed examination. Any determination of visual acuity was a luxury, any record of the visual field a bonus. Interpretation of such indefinable a finding as venous tortuosity or blurring of a disc margin varied with the observer. Children with retinal hemorrhages were often given intensive therapy in other institutions and the hemorrhages had disappeared by the time the patients came to our clinics. All of this made it virtually impossible to establish mathematically the incidence of ocular complication in the disease. Nevertheless, we finally concluded that few sufferers from cystic fibrosis die without showing, at least terminally, definite evidence of ocular pathology.

A distinction should be drawn between anoxia and hypercapnia. For example, anoxia without hypercapnia is found in idiopathic pulmonary fibrosis, the so-called Hammann-Rich syndrome. In eight of these patients we failed to find retinal changes.[16] The brain represents only 2 per cent of body weight but receives 20 per cent of cardiac output. Increased CO_2 increases cerebral blood-flow 75 to 100 per cent, whereas anoxia increases the cerebral blood-flow only 35 per cent.[17,18] In this connection it is significant that patients with cystic fibrosis respond better to hyperventilation, which reduces hypercapnia, than they do to oxygen therapy, which reduces anoxia.

However much we suspect CO_2 (Figure 15) we cannot pretend that its role in the production of ocular pathology is established beyond cavil. Determination of CO_2 in actual tissue is not possible at present. Until it becomes feasible we can only hope that our current investigation of the shift in normal gradients of blood gases between blood and

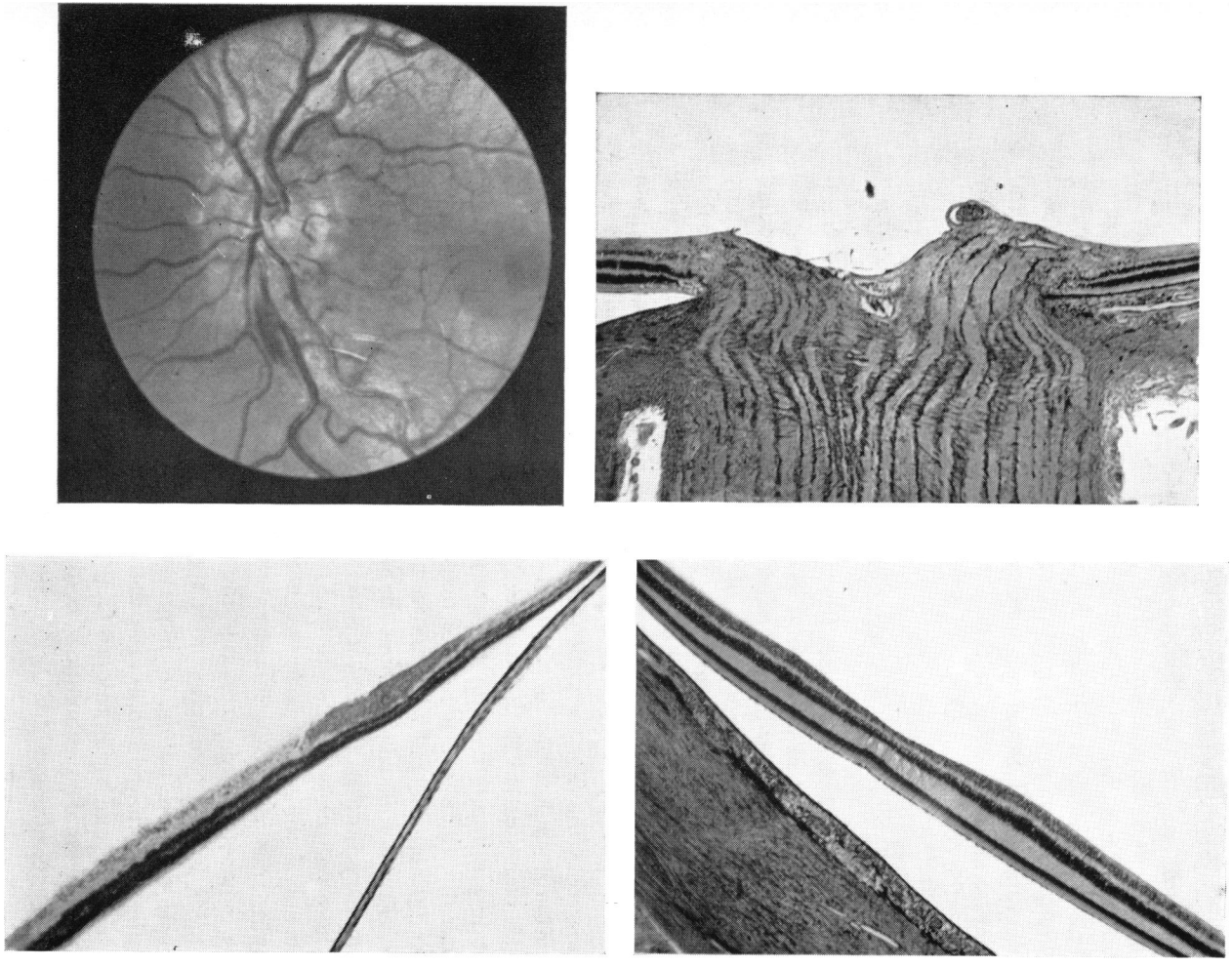


FIGURE 13

Fundus photograph showing hemorrhage, dilated veins. Pathology sections showing hemorrhage, dilated veins, same eye.

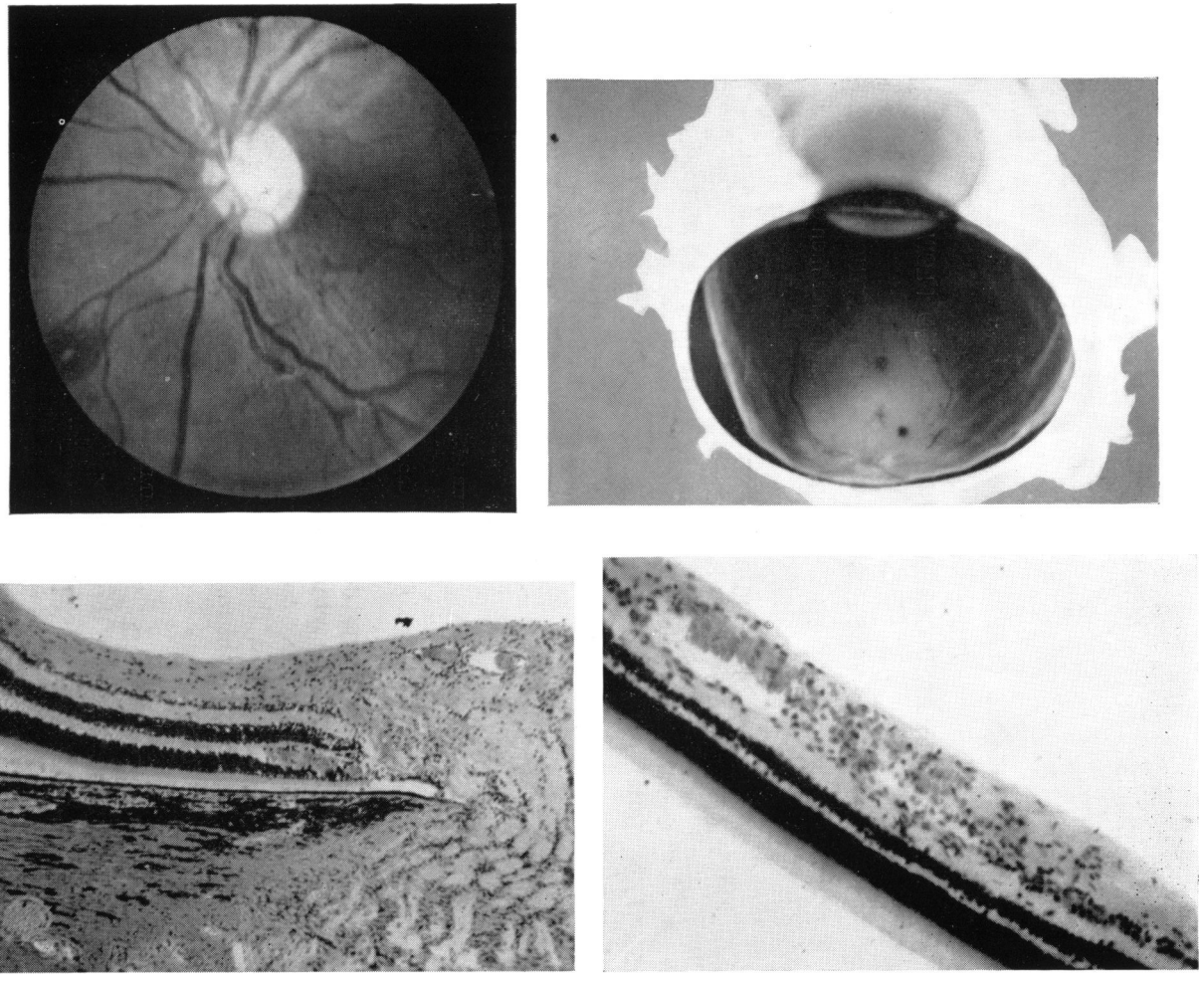


FIGURE 14

Fundus photograph, photograph of globe after opening, showing hemorrhage. Confirmatory pathology sections.

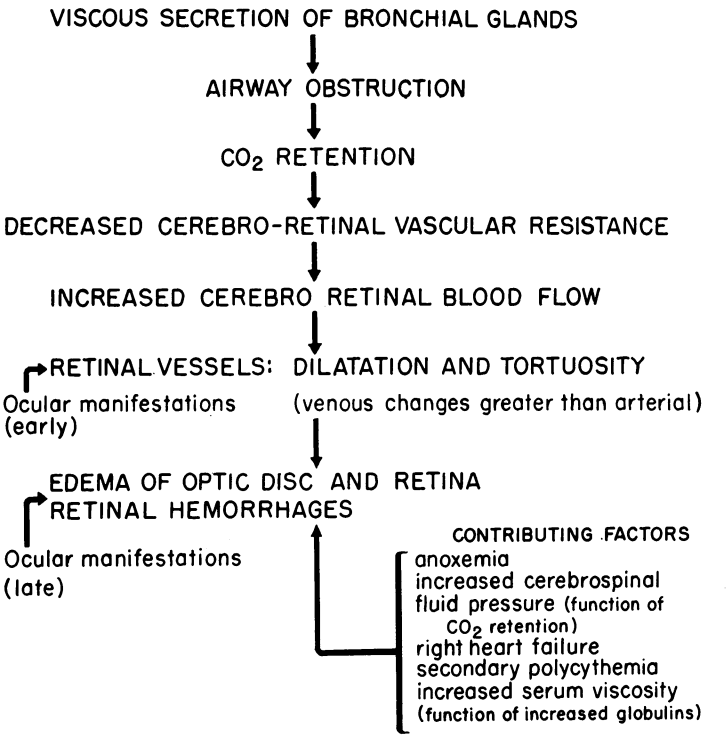


FIGURE 15

Schema of postulated effect upon retina of CO_2 retention in cystic fibrosis of the pancreas.

spinal fluid in the presence of high CO_2 tension will explain some of the changes in the retina and the optic nerve.

The pathologic effect on the eye of antibiotics in large doses is still speculative. We trust that future histopathologic studies will shed some light on the problem.

SUMMARY

1. Cystic fibrosis of the pancreas is usually associated with papilledema, hemorrhage, venous tortuosity, and cystic disease of the macula.

2. These findings are not pathognomonic of the disease, but are due to hypercapnia.

3. The occasional occurrence of retrobulbar neuritis is due to idiosyncrasy for chloramphenicol.

ACKNOWLEDGMENT

The author wishes to thank Doctors Carolyn Denning and Harold Spalter for having borne the brunt of this work. He also wishes to record his indebtedness to Doctor J. A. C. Wadsworth, pathologist, Mr. E. Bethke, artist, Mr. M. Gonzales, technician, and Mr. J. Lafayette, photographer.

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DISCUSSION

DR. LUDWIG VON SALLMANN. With the pleasant memories I have of my time at Columbia-Presbyterian Medical Center, and of the guidance and friendship of Dr. Bruce, it is a joy and honor to be called upon to open the discussion of this paper which deals with one of his major contributions to ophthalmology. In the résumé of his work, Dr. Bruce emphasized two new points which relate to ocular complications observed in patients with cystic fibrosis of the pancreas and treated with a chemotherapeutic agent—that is, the role of hypercapnia in the development of fundus pathology and the probable implication of the therapeutic agent, chloramphenicol, in producing damage to the optic nerve.

At N.I.H., Dr. Di Sant-Agnese, in charge of the cystic fibrosis program and an outstanding investigator of this disease, has the impression that hypercapnia occurs predominantly in terminal stages, but blood gas studies have not been carried out in a systematic way and therefore a definite statement has to be deferred. Throughout the years, members of the eye branch have examined the young patients and, in their efforts, have met the obstacles to thorough studies mentioned by Dr. Bruce. Among 200 patients, optic nerve disease was observed in six children and here, too, circumstantial evidence for correlating the lesion with the prolonged use of the chemotherapeutic agent at high doses was strong. Two of the patients with the picture of complete, or partial, optic atrophy but without marked retinopathy came to autopsy. The following slides obtained from Dr. Vernon Wong, Clinical Associate of the Ophthalmology Branch, show the extent of nerve degeneration accompanied by the disappearance of the ganglion cells and reduction of nerve fiber layers in the retina. The first two slides, at two different magnifications, illustrate the almost complete disappearance of axons of the optic nerve when stained with the Bodian silver technique. Inflammatory changes were absent. The brother of this patient did not exhibit eye complications when he died of the same disease after similar therapy. His normal optic nerve is shown for comparison. In the second patient, with temporal pallor of the optic disc, destruction of the neural elements was essentially confined to the papillomacular bundle and could be followed back to the chiasma.

As in Dr. Bruce's cases, the sudden onset of the visual difficulties was striking and unusual for amblyopias produced by prolonged exposure to a toxic agent. Even more puzzling was the return to normal visual function despite continuation of treatment in one of Dr. Bruce's patients. Similar observations were briefly reported in an abstract article by Dr. N. N. Huang in four out of five patients. In one of our six patients the vision appeared to have improved moderately without interruption of chloramphenicol medication.

Both these unusual features deserve further consideration. Dr. Bruce alludes to an idiosyncratic response as the underlying mechanism of the

optic neuritis. The relation of the time course of treatment and of the impairment or loss of vision, I feel, might be better explained by assuming a hypersensitivity state in which accumulation of the drug could have been modified by conditioning factors in the pathologic events to trigger the neurotoxic effect. With all that was learned in the last decade of toxic side actions of extremely effective therapeutic agents, a discussion on such phenomena in these patients is bound to be of great interest and I am certain that Dr. Bruce has thoughts on it from which we could learn.

DR. P. J. LEINFELDER. I have been interested in Dr. Bruce's paper since I first heard of it at the Academy meeting last fall. I was struck by the similarity of the descriptions and the pictures to the entity that I have thought of for a long time as being cyanosis retinae.

In my experience, cyanosis retinae occurs under three circumstances: first, when there is a disease of the blood such as primary, secondary, or idiopathic polycythemia; secondly, when there is disease of the lung, such as chronic emphysema, cystic fibrosis of the pancreas, or advanced carcinoma of the lung; thirdly, when there is great stress in the cardiovascular system. Pictures exactly similar to those presented by Dr. Bruce can be seen in patients with these three categories of disease.

I would like to add also that in selected patients the disease comes and goes with the degree of activity of the patient, and I have seen a patient who was in bed in the morning, whose fundus looked entirely normal to me, whom I saw again in the clinic in the afternoon and who had extensive cyanosis retinae.

Therefore, I would like to emphasize the point that Dr. Bruce has already made, that this is not a specific entity for cystic fibrosis of the pancreas but it is a symptom or sign that occurs in those situations that can produce inadequate oxygenation or hypercapnia in the blood.

DR. ROBISON D. HARLEY. Ninety-six patients with cystic fibrosis have been seen in the past five years at the St. Christopher's Hospital for Children in Philadelphia. Ocular changes are frequently observed in the advanced cases and consist of venous engorgement and tortuosity, distension of tiny venicles about the discs, blurred disc margins, and varying grades of papilledema, retinal hemorrhages, and blurred vision associated with central scotoma.

Since the basic course of the disease remains obscure, treatment is directed toward amelioration of symptoms of which treatment of the pulmonary infection is of primary importance in order to prolong the life of the children with the disease.

In patients with advanced cystic fibrosis, chloramphenicol has been found to be more effective than most other agents and proved to be life-saving in some instances. The risk of protracted pulmonary infection is so great that it seemed justified to employ a potent drug for prolonged periods of time. Accordingly, large daily dosages of chloramphenicol, averaging

30 to 50 mg. per kilogram per day, divided into three or four doses, were begun over three years ago in thirty patients. We were aware of its potential toxic effect to the hematopoietic system, but had not been concerned with other side effects until April, 1963, when Denning, Bruce, and Spalter first called our attention to the possibility of development of optic neuritis following long-term therapy of chloramphenicol in four patients with cystic fibrosis.

Bruce stated, in his original article in 1960, "The role that massive antibiotic therapy may play in producing these fundal changes is uncertain." By that time we had encountered visual disturbances in six out of twenty-four cystic fibrosis patients on long-term chloramphenicol therapy. The visual findings were first attributed to advanced pulmonary insufficiency with infection, since we had evidence of hypercapnia and chronic hypoxia.

We now have records on nine cystic fibrosis patients who have developed severe visual disturbances with loss of central vision out of thirty patients treated on chloramphenicol for three to forty months. In the affected patient there occurs characteristically bilateral central scotomata of varying density, extending approximately 7 to 10 degrees from fixation. We have observed not one cystic fibrosis case develop central vision loss unless they were concomitantly on chloramphenicol. There would appear to be an association between the central scotomata and the implied toxicity of chloramphenicol.

Our first patient to develop visual symptoms had been on one gram of chloramphenicol daily for seven months when he developed bilateral central scotomata with 20/400 vision bilaterally. We reasoned that possibly we were observing the toxic effects of chloramphenicol on the optic nerve rather than a complication of cystic fibrosis, so the drug was discontinued. The visual acuity improved at once from 20/400 to 20/20 bilaterally. However, the patient's general condition failed so precipitously without chloramphenicol that it was considered advisable to re-administer the drug despite its apparent toxicity. The patient has continued on chloramphenicol for ten months with 20/20 vision bilaterally.

Subsequently, another patient on long-term chloramphenicol developed central scotomata with 20/200 vision. The vision improved spontaneously without drug withdrawal. The patient developed bilateral central scotomata again three months later, which improved while the patient continued on chloramphenicol therapy. High doses of thiamine chloride were the only additional medication.

Two additional patients with central scotomata improved from 20/200 to 20/20 on high doses of thiamine chloride while chloramphenicol was being maintained. Another patient discontinued chloramphenicol on her own volition when she noticed visual disturbances. Visual acuity improved to 20/20 in three weeks bilaterally, but the patient subsequently died. Two patients developed central scotomata while taking chloramphenicol, but both expired before treatment was begun. Two additional patients

developed persistent central scotomata associated with pallor of the optic discs. The vision has remained at 20/400 despite vitamins B-1, B-12, and systemic steroids.

In summary, nine or approximately one-third of the thirty cystic fibrosis patients on long-term chloramphenicol developed characteristic visual disturbances in the form of bilateral central scotomata with marked reduction in vision. All the patients with visual loss had pain in the lower legs.

One patient improved spontaneously without drug withdrawal and with continued usage of chloramphenicol. Four patients improved with the administration of high doses of thiamine chloride while chloramphenicol was being continued. One patient with bilateral central scotomata improved following cessation of chloramphenicol. Two patients developed central visual loss but expired before treatment was begun. Two final patients have failed to respond even with discontinuation of the drug or any therapy attempted to date, including vitamin B-1, B-12, or cortisone.

We have not observed visual disturbances with central scotomata in cystic fibrosis cases which have been treated with other antibiotics.

The neurotoxic effect of chloramphenicol is suspected but the evidence at the present time suggests that it does not exert its effect directly. Other factors in cystic fibrosis are presently under investigation.

DR. BRUCE. I want to thank the discussants. It is gratifying to have one's views supported by such authorities.

Of course, we know chloramphenicol may be a dangerous drug, and one may question why it is given so widely. The answer is that for some reason the other antibiotics do not seem to be so effective. It is comforting to know that when the patient's life is threatened and a decision must be made between improving vision or allowing the general condition to worsen in most instances treatment by chloramphenicol may be resumed.