Optic neuropathy, chloramphenicol, and infantile genetic agranulocytosis. DAVID G. COGAN,* JOHN T. TRUMAN,*** and TAYLOR R. SMITH.***

Shortly after the introduction of chloramphenicol into the antibiotic armamentarium in the early 1950’s, sporadic cases of optic neuritis occurred in patients under treatment for ulcerative colitis1 and subacute bacterial endocarditis.2,3 Subsequently, optic neuritis was reported in association with chloramphenicol treatment of cystic fibrosis.4 This latter has comprised the most frequent association in recent years. By 1969, forty cases of optic neuritis had been reported, but usually only after treatment with at least 100 Gm. over a period in excess of 6 weeks.5 The incidence of ocular involvement in children treated for cystic fibrosis, is of the order of 3 to 5 per cent.6,7

The eyes of five patients with presumed chloramphenicol optic neuritis have been studied histologically.7,8 All of these patients had cystic fibrosis. The present report documents the clinical course and histopathologic abnormalities in a patient treated with chloramphenicol for infections secondary to infantile genetic agranulocytosis.

Case report. The patient was a 4½-year-old girl with a life-long history of multiple infections, several hospital admissions, and finally death from cardiac arrest and overwhelming sepsis due to complete absence of neutrophiles. She was one of three siblings and the only one in the family to have an abnormal susceptibility to infection.

At age two the patient had presented to medical attention with multiple furuncles and otitis media. The white blood cell count at that time was 6,600 with complete absence of neutrophiles. Bone marrow aspirations showed maturation arrest at the promyelocyte stage with no neutrophilic granule formation. All other marrow elements were normal. Epinephrine stimulation showed no marginating granulocytic pool and a Rebuck skin window showed no granulocytic response. A diagnosis of infantile genetic agranulocytosis (Kostman’s disease) was therefore made.

Antibiotics for the constant infections included at various times penicillin, methicillin, cephalosporin, cloxacillin, gentamycin, kanamycin, and tetracycline. With the development of a large draining groin abscess extending to the peritoneal surface and associated with signs of systemic infection, chloramphenicol 250 mg. three times a day was begun as the only antibiotic to which this strain of Escherichia coli was sensitive. In an attempt to mitigate the known marrow toxicity of chloramphenicol, oxymethalone 50 mg. per day was begun simultaneously.

Eight weeks after beginning chloramphenicol, the hemoglobin had fallen from 8 Gm. to 6 Gm. requiring transfusion; white blood cell and platelet count remained unchanged. No visual abnormality

Fig. 1. Section through one edge of fovea showing complete loss of ganglion cells. Hematoxylin-eosin stain.

Fig. 2. Section through periphery of retina showing preservation of a solitary ganglion cell. Hematoxylin-eosin stain.
was present at that time. Eight weeks later and sixteen weeks after beginning the chloramphenicol she complained of crampy abdominal pain and was noted to be unable to see food on the table or candy in her lap. She began to bump into objects like a blind person and seemed to be unaware of her environment. Apart from the eyes the neurologic examination was negative and the electroencephalograph tracing was interpreted as within normal limits. She complained of crampy abdominal pain but had no signs or symptoms of possible polyneuropathy. The visual acuity was estimated to be reduced to hand movements, bilaterally. The pupils did react to light. The discs were thought to be pale and the margins were blurred with a few peripapillary hemorrhages. A diagnosis was made of papillitis.

The chloramphenicol was replaced by keflin, gentamycin, and vitamin B. Within 5 days the disc swelling was less and the patient was able to visualize objects such as a watch, toothbrush, and comb. In another few days she was able to recognize small objects, such as a ring, at 3 feet but she continued to prefer to examine them close to her face.

After discontinuing the chloramphenicol, her infection worsened. She developed progressive pneumonia and cavitation of the lung. She declined to eat and became severely malnourished. A gastrostomy was done prior to a planned lung resection. Following this gastrostomy the patient was again started on chloramphenicol, 1.1 Gm. per day for 2 days and then 0.65 Gm. per day, since bronchial washings showed persistent E. coli sensitive only to this antibiotic. No change in the visual status was noted after one week. A right upper lobectomy was done two weeks later but the patient developed six cardiac arrest postoperatively and succumbed.

The general autopsy disclosed bronchopneumonia, abscess of the groin, and esophagitis. The brain and spinal cord, examined by Dr. E. P. Richardson, showed: (1) minute and symmetric lesions in the most rostral portions of the substantia nigra with loss of neuronal cells and with focal aggregates of microglia; and (2) severe fiber loss and pronounced gliosis of the fasciculus gracilis, bilaterally, at all levels of the cervical and thoracic cord. Nevertheless, the peripheral nervous system, represented by sections from the brachial plexus and spinal ganglia, showed no abnormalities.

The eyes were fixed in 10 per cent formalin, dehydrated, and embedded in paraffin according to standard practice. Sections were stained by hematoxylin and eosin, periodic acid-Schiff, and Bodian-Luxol Fast Blue.

The two eyes were identical so that a description of one applies to both. The anterior segments showed only the features of an infantile eye: kidney-shape distortion of the lens, vacuolization of iris pigment epithelium without identifiable glycogen, and abortive Lange's fold. The posterior segment, however, showed significant abnormalities in the retina, optic nerve, and choroid.

In the retina the ganglion cells were completely absent from the macular and perimacular regions (Fig. 1) but were at least partially preserved toward the periphery (Fig. 2). The nerve-fiber layer on the temporal or macular side of the disc was also markedly attenuated leaving only a thin lamina with glial cells comprising the inner layer of the retina (Fig. 3). The nerve fibers were better preserved on the nasal side (Fig. 4). The macula showed the common artifactual folding and the pigment epithelium showed the frequent postmortem scuffing and folding but was otherwise not remarkable. The bipolar and photoreceptor layers were morphologically normal.

The prelaminar portion of the nerve head showed mild gliosis and the postlaminar portion showed corresponding gliofibrosis with apparent increase in vascularity of the temporal half of the nerve but relatively good preservation of the nerve architecture on the nasal half. The Luxol Fast Blue stains showed poor preservation of myelin on both sides. There was no gitter-cell reaction and no evidence of inflammation in the nerve or about the vessels.

The choroid was of normal dimensions but
Fig. 4. Higher power view of the remaining nerve fibers on the nasal side of the disc.

showed mild infiltration with pleomorphic cells that varied from round cells to atypical plasma cells having an unusual abundance of cytoplasm and occasional double nucleus. Some extra large cells resembling megakaryocytes were also present.

The primary disease of this patient was infantile genetic agranulocytosis. Approximately 40 cases have been reported in the literature since it was first described in 1956 by Kostman. The characteristic failure to form mature neutrophiles in this condition results in repeated bacterial infections that usually cause the death of the patient within the first few years of life. No case of optic neuritis has previously been reported with it.

The bacterial infection in the present patient was exclusively susceptible to chloramphenicol, and it was used in large doses over a long time. The optic "neuritis" in this patient was similar in its clinical and histopathologic manifestations to that which has been reported in cystic fibrosis. It was not associated with pain, clinically evident polyneuropathy elsewhere, or other symptoms except for the abdominal cramps. The patient was anemic but other cases of optic neuritis have failed to show any relation to the aplastic anemia of chloramphenicol.

The pathogenesis of the chloramphenicol optic neuropathy is obscure. Some evidence has suggested a relation to thiamine deficiency, but thiamine levels in the blood have been normal. Attempts to produce it in rabbits by giving large amounts of chloramphenicol (70 to 180 mg per kilogram per day for 35 days) have been unsuccessful.

Histopathologic examination of the eyes has been previously carried out in five patients with cystic fibrosis and optic neuropathy, presumed to be due to chloramphenicol. These eyes showed symmetric loss of ganglion cells from the retinas and atrophy of fibers in the optic nerves. The present case confirms these findings and supports the cumulative evidence that the lesions are due to chloramphenicol rather than to the cystic fibrosis. The peculiar infiltrate in the choroid of the present case is presumably attributable to the agranulocytosis since it was not present in the cases of cystic fibrosis, but whether it represents aberrant erythropoiesis or an overcharged immunologic response could not be resolved on the histopathologic evidence. The severe fibrosis in the fasciculus gracilis of the spinal cord without corresponding changes in the peripheral nerves suggests, but does not prove, a lesion within the central nervous system analogous to that in the optic nerve.

A case of probable chloramphenicol optic neuropathy is reported in a patient with infantile genetic agranulocytosis. The histopathologic examination of the eyes revealed loss of the ganglion cells from the macular and perimacular region, an atrophy of the corresponding portion of the optic nerve, and a mild infiltration of the choroid with pleomorphic round cells. The spinal cord showed a bilateral fibrosis of the fasciculus gracilis without corresponding lesions in the peripheral nerves.

From the Howe Laboratory of Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School; the Department of Pediatric Hematology, Massachusetts General Hospital; and the Department of Ophthalmic Pathology, Massachusetts Eye and Ear Infirmary, Boston, Mass. Manuscript submitted for publication May 15, 1973; manuscript accepted for publication May 16, 1973.

REFERENCES
An indoleamine-containing cell in chick retina. DOLORES C. HAUSCHILD AND ALAN M. LATIES.

A puzzling discrepancy has arisen over the last two decades concerning the nature and location of biogenic amines within the retina. At the same time that assay techniques have repeatedly demonstrated the presence of both indoleamines and catecholamines, several representative vertebrate retinas, histochemical reports have uniformly described the retinal localization of catecholamines alone. Thus, the nature and extent of catecholamine-containing cells in the retina have been abundantly documented while similar information about retinal indoleamines is lacking. Further, this state of affairs exists despite the acknowledged histochemical documentation of the indoleamine-containing cell groups within the central nervous system. Recently, we have undertaken a study of the ontogeny in the chick retina of cells which contain biogenic amines. In the course of this study it has become apparent that the chick retina is unusual in having within its inner nuclear layer three quite distinct populations of cells: (1) a major population which has none of the fluorescence characteristics associated with cells containing biogenic amines, and (2) two minor populations; one of which displays fluorescence characteristics usually considered indicative of catecholamines while cells in the other population have fluorescence characteristics usually considered typical of indoleamines. The present report documents the occurrence of the latter two types of cells in chick retina.

A total of 30 chicks, 3 each of incubation time 12 to 21 days were treated as follows: following decapitation, the eyes were removed from their sockets and quick-frozen in liquid isopentane cooled to -125°C in a liquid nitrogen bath. Once frozen, the eyes were transferred to a modified molecular-sieve, freeze-drying apparatus where they were allowed to dry at ~35°C for one week. Thereafter, they were processed for fluorescence of catecholamines by a standard method. After paraffin embedding, histologic sections were viewed in a fluorescence microscope equipped with a BG12 exciter filter and a Zeiss 50 barrier filter.

In addition to the normal animals listed above, the following drug experiments were performed: (Group A) five 21-day embryos were injected intraperitoneally with reserpine (reserpine, Sigma Chemical Co., St. Louis, Mo.), 2.5 mg per kilogram per 24 hours; (Group B) six 21-day embryos were given intraperitoneal reserpine, 5 mg per kilogram per 24 hours and then also given Tranylcypromine (trans-2-phenylcyclopropylamine, Sigma Chemical Co., St. Louis, Mo.) 5 mg per kilogram per 5 hours; and (Group C) six 21-day embryos were injected intraperitoneally with DL-para-chlorophenylalanine (DL-p-Chlorophenylalanine, methyl ester, hydrochloride, Calbiochem, Los Angeles, Calif.) 200 mg per kilogram per 17 hours.

From 14-days onward, in the normal chick retina, green, fluorescent cells are visualized in the inner-nuclear layer cell row immediately adjacent to the inner plexiform layer (Fig. 1). These cells bleach slowly in the ultraviolet light. In the 16-day embryo and in all embryos observed thereafter, yellow, somewhat smaller cells are observable in a deeper portion of the inner nuclear layer, located three or four cell rows from the inner plexiform-inner nuclear junction. The yellow fluorescence of these cells fades rapidly in the ultraviolet light (Fig. 1). Both types of cells are easier to visualize in chicks treated with a monoamine oxidase inhibitor.

The fluorescence characteristics of the first type of cell fit well with those previously described in avian retina by Ehinger and are generally considered typical adrenergic retinal cells, i.e., cells that contain dopamine or noradrenaline in their cytoplasm. The fluorescence characteristics of the second type of cell, both the yellow color and the rapid photodecomposition, are generally thought representative of fluorophores derived from serotonin and other indoleamines.

It was to test the validity of these histofluorometric observations that the pharmacologic experiments were undertaken. Animals from Group A,