CEREBRO-RETINAL DEGENERATION DUE TO CARBON DIOXIDE POISONING*†

BY

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GEOLOGISTS have long known that carbon dioxide may collect in underground workings and in sufficient concentration may cause loss of consciousness and death (Geological Survey and Museum, 1951). It is known that the gas is likely to be expelled when the barometric pressure falls abruptly to low levels. Asphyxiation by carbon dioxide produced in the process of fermentation in breweries and during wine-making has also been recorded. This paper presents the clinical features and the pathological findings in the retina and the brain of a man who was asphyxiated by carbon dioxide.

The incident under consideration occurred on December 28, 1960, while an artesian well, 603 feet deep, in central London was being dismantled. The barometric pressure fell sharply to 992.6 millibars (which is a low level for the British Isles) during a week-end when work was suspended, and an asphyxiating gas collected in the well-head chamber. A record of the barometric pressure over this period is shown in Fig. 1.

FIG. 1.—Record of barometric pressure in London during December, 1960, and January, 1961.

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The men who entered the chamber when work was resumed after 3 days collapsed immediately, as did those who went to their assistance. They were rescued after 10 minutes with the aid of breathing apparatus, but three were found to be dead, and one—the last to enter the chamber—was in profound coma.

He was taken to University College Hospital, London, where he was found to be deeply unconscious; his blood pressure was 115/70, his pulse rate was 80 per minute, and his respiration was regular. Investigation of the central nervous system showed normal reflexes, the plantar reflexes were flexor, and muscle tone was normal. There were no eye movements, the pupils reacted to light, and the fundi were normal; 6 hours after admission he developed marked spasticity with extensor plantar responses; this was thought to be due to cerebral oedema causing mid-brain compression. An intravenous infusion of hypertonic urea was given, which abolished the extensor plantar responses and reduced the spasticity. A few hours later the patient developed a pyrexia of 105°F. (rectal), which was treated with damp sheets. Severe shivering attacks which followed were treated by intramuscular injections of chlorpromazine.

Next day his general condition was good and his temperature was 97°F. Tracheotomy was undertaken which greatly facilitated his breathing. Lumbar puncture showed the cerebrospinal fluid to be slightly discoloured, with a pressure of 19.3 cm. Examination of the central nervous system at this stage showed marked spasticity; the pupils were fixed and dilated. There was a characteristic decerebrate posture of over-flexion and over-pronation of the fore-arms, adduction at both shoulders and extension of the legs which was maintained until he died.

6 months after the accident an electro-encephalogram (EEG) showed that the electrical activity was of very low voltage and arrhythmic, most of it being about 4 c/s. No alpha rhythm was seen. The record from the left hemisphere was a little flatter than that from the right. There was no change in the EEG when the eyes were held closed nor when the patient was tested with painful stimuli.

The patient lay with his eyes open much of the time, apparently awake. He remained completely unresponsive, had to be fed by gastric tube, and was doubly incontinent until he died 11 months after the accident.

Post Mortem Studies

The *post mortem* examination was done by Prof. F. E. Camps. The eyes were sent to Prof. N. Ashton, Department of Pathology, Institute of Ophthalmology, London, and the brain to Prof. P. M. Daniel, Department of Neuropathology, Maudsley Hospital, London, for histological examination.

THE EYES

The eyes were received fixed in 10 per cent. formol saline. The left eye was embedded in celloidin, and routine sections cut. The retina of the right eye was digested according to the technique of Kuwabara and Cogan (1960) as modified by Ashton (1963).

Left Eye

Macroscopical Examination.—The eye was opened in the horizontal plane, a pale optic disc was noted.

Microscopical Examination.—The corneal epithelium was absent centrally and at the limbus there was a chronic perivascular infiltration. The corneal stroma was hypercellular and showed early vascularization; keratic precipitates were present on the corneal endothelium. The filtration angle was open and acute inflammatory cells were found in the anterior chamber. There was no significant abnormality of the iris, lens, or ciliary body.

The retina showed extensive loss of the ganglion cells and there was also some atrophy of the nuclear layers (Figs 2 and 3, opposite). There was a rod and cone exudate which was probably a *post mortem* change. The optic nerve was gliosed, and at the disc (Fig. 4, opposite) the central retinal artery showed marked thickening of its walls. The choroid and sclera appeared normal.

FIG. 2.—Section of retina showing extensive loss of ganglion cells. Haematoxylin and eosin. $\times 120$.

FIG. 3.—High-power view of Fig. 2. No ganglion cells are present in the inner layer. Haematoxylin and eosin. $\times 360$.

FIG. 4.—Section of optic nerve, showing gliosis of optic nervehead. Weigert stain. $\times 45$.

Right Eye

At the disc the digested retina showed obliteration of the superficial capillaries and in the rest of the retina there was loss of the endothelial cells, but the intramural pericytes appeared normal. There was no aneurysm formation or endothelial proliferation (Fig. 5).

FIG. 5.—Retinal digest, showing loss of endothelial cells. Periodic acid-Schiff. $\times 428$.

Comment

- (1) The anterior segment changes in the eye were those of exposure keratitis, corneal ulceration, and hypopyon.
- (2) The outstanding abnormalities were in the retina, where there was absence of the ganglion cells, atrophy of the nuclear layer, replacement gliosis, and absence of the endothelial cells in the retinal digest.
- (3) The effects of CO_2 on the retina were not specific in any way.

THE BRAIN (Maudsley, No. 1894).

The brain weighed 998 g. and showed severe atrophy, more marked in the posterior two-thirds of the hemispheres. The cerebellum was also severely atrophic.

Coronal sections through the hemispheres showed gross dilatation of the ventricles. The cortical ribbon was thin and yellow, particularly in the depths of the sulci (Fig. 6, opposite). The cortex of the insula, the antero-medial surface of the frontal lobe, and the hippocampus were relatively spared. The basal ganglia were shrunken and necrotic. The white matter was chalky-white throughout. The basal part of the pons was infarcted.

Microscopic Examination.—There was severe destruction of the cerebral cortex over large areas. Ammon's horn was only slightly affected. The boundary zones between arterial territories were *not* especially severely affected. The white matter was severely demyelinated and was filled with lipid-laden phagocytes. There were organized areas of infarction in the putamen, globus pallidus, thalamus, midbrain, and pons. Secondary degeneration of the descending tracts was well marked.

The cerebellum showed almost total loss of Purkinje and granule cells in all areas. Recognizable cerebellar cortex was present at the tips of the folia only (Fig. 7, opposite). The dentate nucleus showed cell loss and gliosis.

In the spinal cord there was degeneration in ascending as well as descending tracts. (No posterior root ganglia were available for examination).

FIG. 6.—Coronal section through cerebral hemispheres. The whole of the ventricular system is dilated. There is cortical necrosis over the convexity of the hemispheres, elsewhere the cortical ribbon is narrowed. The basal ganglia are shrunken and contain cystic areas of organized infarction.

FIG. 7.—Cerebellum. Granule cells and Purkinje cells have completely disappeared except at the tips of the folia (arrows). Nissl. $\times 25$.

Discussion

Accumulations of carbon dioxide are found in the region of chalk strata, but the means by which the gas is produced is not definitely known. It has been suggested that it may be due to the action of sulphuric acid on chalk, the acid forming underground as a result of the decomposition of iron sulphides (Department of Scientific and Industrial Research, 1938). Accumulations of the gas depend largely on the increase with lower barometric pressure and may change from hour to hour.

It was concluded that the asphyxiating gas in the well-head chamber was carbon dioxide, which is the gas most likely to be encountered in the course of work on wells (Institute of Civil Engineers, 1951). It is of interest that there is a record of carbon dioxide having been emitted from this particular artesian well during its construction in 1924. Other gases which are known to occur in wells include carbon monoxide and hydrogen sulphide. Carboxyhaemoglobin, however, was absent at the autopsy of the men who died and the smell of the H_2S gas was never detected. Oxygen must inevitably have been lacking since carbon dioxide is heavier than air and displaces it upwards and, therefore, anoxia cannot be completely excluded as being entirely responsible or even a contributory cause of cerebral damage in this case.

There is no record in the literature of a histological study of the effects of carbon dioxide on the eye. It has been shown that the vessels of the mature retina dilate on exposure to carbon dioxide and return to their normal calibre on withdrawal of the gas. Carbon dioxide injected into the eyes of rabbits is absorbed within one hour without injury to the eye (Grant, 1962).

The effects of anoxia on the retina have, however, been studied in greater detail. Turnbull (1948) produced retinal ischaemia in rats by centrifuging the animals until they were unconscious. He found that centrifuging at plus 10 G. for 3 minutes caused irreversible changes in the retina. The ganglion cell layer was the most severely affected followed by the bipolar cell layer. The outer nuclear layer was the least affected. Sections of the retina examined after 5, 7, 14, and 21 days showed a progressive loss of ganglion cells.

Smith and Baird (1952) produced ischaemia of the retina in two ways. The first method was to cut the central retinal artery and the long and short posterior ciliary vessels (Wagenmann, 1890), and the second method was to raise the intra-ocular pressure to 100 mm. Hg by the injection of sterile normal saline into the eye. The retinae were studied immediately after these procedures and at selected time intervals. Degenerative changes were observed in the bipolar cells after 15 to 20 minutes, and in the ganglion cells and rods and cones after 20 to 30 minutes. The retinal changes were similar irrespective of the method of producing the retinal ischaemia. Eyes were examined after 21 days and the changes observed in the retina were dependent on the period of ischaemia. Depriving the eye of blood for 10 minutes or less produced no changes in the retina, while ischaemia of 20 to 30 minutes caused degeneration of the ganglion and bipolar cells.

Reinecke, Kuwabara, Cogan, and Weis (1962) produced ischaemia of the retina in cats by raising the intra-ocular pressure above the systolic pressure of the central retinal artery. Periods of ischaemia of less than $1\frac{1}{2}$ hours failed to destroy the retina. Shorter periods of ischaemia caused endothelial proliferation of the retinal vessels. Ischaemia of $1\frac{1}{2}$ hours or more resulted first in loss of the ganglion cells, then increasing periods of ischaemia resulted in loss of the rod and cone nuclei and finally bipolar cells. Death of endothelial cells and "mural cells" occurred following an initial proliferation. In the final stages, the retinal capillaries were represented by fine fibrous tissue strands.

A systematic study of the histopathological effects of CO_2 on the central nervous

system has not been carried out. Stephens (1951) exposed rats to 38–43 per cent. CO₂ for periods of 2·5 to 19·3 hours and to 6 to 10 per cent. CO₂ for periods up to 166 days. The most severe effects both in the acute and prolonged experiments were present in the thalamus, brain stem and spinal cord. The point was stressed that structures exhibiting the greatest physiological activity also showed the greatest histopathological effects.

Meessen (1948) found that 48 hours' exposure to 16 per cent. CO₂ resulted in histopathological changes in the nerve cells of the medulla oblongata and the cerebral cortex, and pronounced effects in the various nuclei of the brain stem. On the other hand, Schaeffer (1963) did not note significant histopathological changes in guinea-pigs and rats that had been exposed to 1·5 per cent. CO₂ for 42 days and in guinea-pigs exposed to 15 per cent. CO₂ in air for up to 7 days.

The question arises whether the brain damage suffered by this patient was due to the lack of oxygen in the air which he breathed or to the excess of carbon dioxide. There are two important features in the pathology of the central nervous system suggesting that anoxia alone was not responsible for the lesions found; first the wide indiscriminate distribution of the damage, and secondly the severity of the individual lesions. In cases of anoxia, a so-called selective vulnerability has been described, which results in the loss of nerve cells followed by gliosis, only in certain areas of the brain. Large areas of total necrosis were present in the cerebrum involving not only most of the cerebral cortex but also white matter, all the basal ganglia, mid-brain, and pons—features not seen after anoxia (Meyer, 1963), hypotension, or circulatory collapse. Similarly, while Purkinje cell loss in the cerebellum is common after anoxia, the almost complete loss of these cells and of granule cells seen in the present case, is most unusual. In addition, degeneration of the posterior columns of the spinal cord has not been described in cases of anoxia.

Thus it seems that anoxia alone cannot account satisfactorily for the changes in the central nervous system and it may well be that carbon dioxide itself has a histotoxic action. The effects of CO₂ on the eye, however, are not specific and the histopathological changes in our case are similar to those caused by anoxia.

Summary

The clinical features and the pathological findings in the retina and brain of a man who was asphyxiated by carbon dioxide are described and discussed.

We are indebted to Prof. N. Ashton, who first examined and reported the histological sections of the eye, and who has allowed us to publish the details, to Dr. S. J. Strich, Department of Neuropathology, Institute of Psychiatry, Maudsley Hospital, for the brain report, and to Dr. Heaf, University College Hospital, for allowing us to examine the clinical notes of the patient. Prof. F. E. Camps kindly permitted us to examine the *post mortem* findings of the present case and was instrumental in referring the specimens for histological examination. We are also grateful to Mr. E. J. Edwards for the details of the artesian well and to the Director of the Geological Museum, London, for the information on the production of carbon dioxide in wells. We should like to acknowledge the assistance given by the Meteorological Office and the Medical Illustration Departments of the Institute of Ophthalmology, and the Institute of Psychiatry, The Maudsley Hospital, London.

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