THE JOURNAL OF NEUROLOGY AND PSYCHOPATHOLOGY.

VOL. I.

AUGUST, 1920.

No. 2.

Original Papers.

A CONTRIBUTION TO THE HISTOPATHOLOGY OF CARBON-MONOXIDE POISONING.

BY R. M. STEWART, PRESTWICH.

POISONING by carbon monoxide is of considerable practical importance in consequence of the greatly increased use of coal gas in modern industrial occupations. It is the cause of death in the vast majority of colliery disasters, and is often responsible for serious illness among iron and steel workers; nor can it be doubted that this agent may have much to do with the chronic ill health seen in laundry workers, cooks, factory hands, and, indeed, among all those employed in occupations where coal gas is used for power, heating, or cooking purposes.

Its symptoms are regarded by Haldane as being essentially those of want of oxygen, which is brought about by the displacement of the oxygen of oxyhæmoglobin by carbon monoxide, with the resulting formation of a more stable compound, carboxyhæmoglobin. According to his observations, carbon monoxide acts not so much as a poison, but as a physiological indifferent gas, apart from its one fatal property of uniting with hæmoglobin. In this way the blood is deprived of its oxygen-carrying power, a condition of anoxæmia is established, and serious or fatal damage inflicted on the tissues. There are, however, a number of workers who do not subscribe to this view, but affirm on the contrary that death is not so much the result of a diminished supply of oxygen as of a specific action of carbon monoxide on the nervous system. It has been pointed out that in carbon-

monoxide poisoning there is no dyspnœa as there is in ordinary asphyxiation, and in animals poisoned experimentally breathing proceeds in an almost normal manner (Gippert). The respiratory centre does not appear to respond to the want of oxygen by increase of respiration, from which it may be inferred that carbon monoxide has a specific action on the nerve centres. In the characteristic train of symptoms following the inhalation of carbon monoxide, or exposure to gases containing this compound, the most important are those relating to the functions of the nervous system. Headache, vomiting, impairment of the higher mental functions, of the special senses, and of voluntary motor power, may be frequently observed; in severe cases, where the saturation of carbon monoxide exceeds fifty per cent, loss of consciousness and death usually occur. The remote effects seen in patients who survive are of a very varied character; but mental and nervous disorders are conspicuous in all, the former comprising varying degrees of dementia or amnesia, and the latter spastic paralysis or peripheral neuritis. Mott, who examined the brain of a woman who died after inhaling illuminating gas, observed enormous numbers of small capillary hæmorrhages throughout the white matter of the centrum ovale, in the corpus callosum, and, to a less extent, in the brain stem, various chromatolytic changes in nerve-cells, and widespread fatty degeneration of the endothelial cells of the smaller vessels. In this case pneumonic consolidation was also found, and it is possible that a pneumococcic toxæmia was associated with the cause of the hæmorrhages. Punctiform hæmorrhages have also been described by a number of other observers, but on the other hand they are sometimes absent; thus Davies reported that he was unable to observe any in the brain of a miner who succumbed to carbon-monoxide poisoning in the Senghenydd disaster of 1913. In the majority of fatal cases which have been the subject of pathological investigation, death has occurred within a period of four to seven days; to determine to what extent the neurone suffers permanent damage and, in general, how the nerve-fibres and their enclosing myelin sheaths react to the impoverished oxygen supply, it is necessary to examine material from cases in which the fatal issue has been delayed for several weeks.

The writer has been fortunate in having had the opportunity of examining tissue from every part of the cerebrospinal axis of a patient who died from the effects of gas poisoning on the twenty-fourth day of his illness. Histological examination revealed the presence of an intense and universal myelin degeneration, bilateral softening in the basal ganglia, and a widespread cortical softening, strictly confined to the deeper layers of the grey matter. Such a peculiarly situated

encephalomalacia has apparently not been hitherto described, and it is chiefly for this reason that the present contribution is made.

Clinical History.—W. A., male, engineer, age 55. Admitted to the County Asylum, Prestwich, Dec. 10, 1913, with a history that he had been restless and nervous for about one month, but had remained at work up to the day before his attempted suicide (Dec. 7). When 40 years old he had had Bright's disease, and was then depressed for a fortnight.

ON ADMISSION.—He was in a very debilitated state, with cyanosed lips, sordes on teeth, and obstinate constipation; temperature 98.8° , pulse-rate 96. Urine: sp. gr. 1030, acid; deposit of urates; traces of sugar and albumin. Nervous system: pupils slightly unequal; normal reaction to light. Knee-jerks exaggerated. Slight wasting of small muscles of left hand. Mental state: he lay passively in bed with eyes closed, made no reply to questions, and was fed with difficulty. During the succeeding four days he remained in the same condition of torpor, apparently quite oblivious to his surroundings. On Dec. 15 his temperature rose to 100° , and he became restless, occasionally throwing his arms about, and crying out suddenly. Lumbar puncture was performed on Dec. 20; a marked lymphocytosis and a positive Noguchi reaction were present. Two days later he appeared somewhat better, and made efforts to speak, but without success. Tendon reflexes were brisk: plantars normal; no sphincter control. There was now more distinct wasting of the thenar and hypothenar eminences of the left hand. Dec. 26, pulse became soft, compressible, and difficult to count, and wasting of the small muscles was now observed in both hands. Dec. 30—the day of his death—he lay with his head retracted and limbs flexed, moaning constantly. Temperature 98° , pulse 84, and respirations 32. Death at 6.45 p.m.

Post-mortem Appearances.—Autopsy thirty-nine hours after death; the weather was very cold, and the body was therefore in a good state of preservation.

There were no external changes of importance, and the blood was normal in appearance. Dura mater was normal, and pia arachnoid hyperæmic, diffusely thickened, and of milky colour. This thickening was evenly distributed over the whole convex surface, and also at the base. The brain weighed 1340 grms.; the convolution-pattern was complex, and there was no obvious cortical atrophy. Careful scrutiny of the cortex in section showed the presence of an almost continuous line, greyish-white in colour, situated nearer the deep than the external surface, and suggestive of a cortical softening remarkably sharply defined, but apparently universal in its distribution. In the white matter the only change noted was prominence of blood-vessels. There was an entire absence of punctiform hæmorrhages throughout the cerebrum; of ventricular dilatation; and of ependymal granulations. The globus pallidus contained a small but obvious softening, darker in colour than the surrounding tissue, which had a friable, pitted appearance. Situation, shape, and appearance of affected area corresponded exactly on the two sides. The large arteries at base were healthy. Spinal cord presented no naked-eye abnormality. Both kidneys much reduced in size, firm, and cirrhotic, with moderate degree of cortical atrophy. Other organs showed no noteworthy change.

Microscopical Examination of the Nervous System.—Preliminary fixation by formalin and alcohol; the cerebral gyri were examined in

every region of both hemispheres, and in addition sections were made from basal ganglia, cerebellum, red nucleus, brain stem, and spinal cord. Certain cranial nerves were examined. For the preparation of the sections I am indebted to Mr. H. Wisken, late laboratory assistant.

The Cerebral Cortex. The Pia Arachnoid.—The meshes of the pia contain congested blood-vessels, in some of which the red blood-corpuscles show a basophil reaction; partial or complete hyaline thrombosis has occurred in many places. The cells of the pial connective-tissues have undergone moderate proliferation, and adventitial infiltration may be seen in certain situations. Plasma-cells, fibroblasts, polyblasts, and rod-cells can be identified; no polymorphonuclear leucocytes or mast-cells are present.

The Area of Softening.—A close examination of vertical sections of the unstained cerebral cortex with a lens, or even with the naked eye, shows the presence of a narrow stratum, greyish-white in colour, in the deeper part of the grey matter. It is present throughout the whole cerebral cortex, and both hemispheres participate to an equal extent. With a low power it is at

FIG. 1.—Cortex. Right ascending frontal gyrus, showing the zone of softening in the infragranular layers. Frozen section stained with scharlach-R.

FIG. 2.—Cortex. Right first temporal gyrus, showing similar appearances. Frozen section stained with scharlach-R.

once obvious that in every area of the cortex there exists a zone of softening, and further, that without exception this occurs only in the deeper or infragranular layers of the grey matter. (*Figs. 1, 2.*) It can be followed over wide areas as a continuous unbroken line, showing little or no variation in its contours. In some situations, however, it is interrupted, giving an appearance of multiple foci of softening, with narrow tracts of unsoftened grey matter isolating these areas one from the other. The usual site of this morbid process is in the third and fourth cortical layers (Brodmann's nomenclature), as in nearly every situation a narrow zone of more normal grey matter separates it from the medullary substance.

The appearance of a frozen section stained with scharlach-R is very striking; the brilliantly-stained orange-red fatty droplets crowded together in the area of necrosis form a conspicuous band of colour, contrasting with the paler and more normal tissue above and below it. The necrotic character is clearly indicated by the presence in it of a great increase of stainable

fat. (Figs. 3, 4.) With Nile-blue sulphate-A the fat-globules stain deep blue, no red-stained fat being seen. The application of Marchi's method gives the appearance of brownish-yellow globules, intensely black droplets being rarely seen.

It is important to observe that the process of softening is a partial one: the picture is not that of an area in which all structural form is lost; disintegrating lipoid substance is present in great abundance, but the process has not gone on to complete autolysis. The necrosed tissue stains rather diffusely with acid dyes. In it one can observe a partial disappearance of the more highly differentiated elements—the ganglion cells—sparing the neuroglia and vessels in such a way that the architecture of the area is to some extent preserved. Here and there ghost-cell outlines are visible, and the majority of surviving nerve-cells have suffered great distortion in shape and position; their processes have also disappeared. Axis-cylinders can be traced from the white matter through the lowest cortical layer to the zone of softening, where they abruptly disappear. In this way

FIG. 3.—Cortex. Left ascending parietal gyrus: frozen section stained scharlach-R, showing stainable fat in intracortical zone of necrosis.

FIG. 4.—Cortex. Left ascending parietal gyrus, showing under a higher magnification the fatty droplets. The white matter is below. Frozen section stained with scharlach-R.

the lower boundary of the area is clearly defined. Both above and below it are nerve-cells preserving to a certain extent their normal columnar arrangement; they are in all stages of subacute decay, and in many instances surrounded by satellite cells.

The neuroglia tissue shows an active cellular proliferation; numerous cells having the morphological appearance of *Stäbchenzellen* are present, and others, resembling fibroblasts, occur in great numbers. At the edges of the softened area there is no dense zone of cellular proliferation such as one is accustomed to see at the margins of a small cerebral softening.

There is an appearance of increased vascularity owing to the formation of new capillary vessels, which can be seen sprouting in every direction. Many small vessels show adventitial proliferation, and contain hyaline thrombi; on the other hand, in many situations the vessels contain unaltered and discrete red blood-corpuscles.

In the regions of the cortex, above and below the zone of softening,

both parenchymatous and interstitial changes are found. The surface neuroglia layer is slightly thicker than normal, and elsewhere there is a marked increase in neuroglia-cells. Congested vessels frequently filled with hyaline thrombi are found, and the Virchow-Robin spaces are filled with small round cells; plasma-cells occur in small numbers.

The White Matter.—There is widespread degeneration of the myelin sheaths of nerve-fibres, enormous numbers of fine black droplets being scattered throughout the medullary substance; they are particularly abundant in the neighbourhood of vessel-walls. The axis-cylinders exhibit various morbid changes; frequently they stain intensely with hæmatoxylin and eosin. The neuroglia-cells are increased in numbers, and the vessels are dilated and often filled with hyaline thrombi. Careful search does not reveal the presence of free hæmorrhages or foci of softening.

The Basal Ganglia.—The globus pallidus is filled with very numerous *Körnchenzellen* (Fig. 5); in the putamen they are less numerous, and tend to occur in groups, often in the neighbourhood of vessels. The internuncial

FIG. 5.—Körnchenzellen in right globus pallidus. Marchi's stain.

FIG. 6.—Longitudinal section of the right vagus nerve, showing intense Marchi reaction. Marchi's stain.

fibres and those traversing the nuclei stain an intense black. Many of the larger blood-vessels are filled with red blood-corpuscles and partly-formed thrombi; others show little or no deviation from the normal. The neuroglia nuclei are greatly increased in number, and the nerve-cells are profoundly affected; many have disappeared, and others are in advanced stages of decay.

Basal Perforating Arteries.—There is a certain amount of adventitial proliferation and cellular infiltration; some vessels can be found filled with thrombosed red blood-corpuscles.

The Optic Thalamus.—No hæmorrhages or areas of softening can be found, but hyaline thrombosis occurs with great frequency in the larger vessels. Marchi preparations show fine black granules throughout its substance.

The Cranial Nerves. Optic.—Sections from Marchi preparations show a diffuse distribution of fine blackened globules of altered myelin; the appearance is very similar to that seen in the medullary substance of the

cerebral hemispheres. *Facial*.—There is much more evidence of myelin degeneration, the blackened granules being numerous and of large size. *Vagus*.—In comparison with the other cranial nerves the vagus shows an intense myelin degeneration; hardly a fibre has escaped, the section staining almost uniformly black. (*Fig. 6.*)

The Cerebellum. Cortex.—The pial vessels are congested, and many are surrounded by small round cells. Immediately beneath the pia mater are large numbers of colloid bodies. Hyaline thrombosis is present, but no hæmorrhages or areas of softening are visible. The Purkinje cells show pronounced chromatolytic changes, the majority appearing pale, homogeneous, and without Nissl bodies. Marchi sections show considerable myelin degeneration, uneven in its distribution.

Central Nuclei.—There is marked myelin degeneration in the neighbourhood of the nucleus dentatus; the nerve-cells are heavily pigmented, and show various stages of chromatolysis.

The Red Nucleus.—In the upper part of the midbrain there is a widespread myelin degeneration, which is particularly marked in the fibres of the third nerve as they traverse the nucleus ruber. The smaller nerve-cells of the nucleus show diffuse staining and a disappearance of chromatolytic substance.

Pons Varolii and Medulla Oblongata.—There is a diffuse and intense Marchi reaction, which is particularly well seen in the pyramids, in the solitary bundles, and in the cranial nerves in their intramedullary course. The nerve-cells are for the most part abnormal; the cell body is usually swollen, and shows a degeneration of the stainable substance into dust-like particles in the neighbourhood of the nucleus, which is usually dislocated to one side. The changes in the vagal nuclei do not appear to be more pronounced than those in other situations.

The Spinal Cord. Nerve-cells.—The ganglion cells show a fairly advanced chromatolysis—for the most part perinuclear. It is more especially the large nerve-cells that are affected; indeed, many have completely disappeared. Others are reduced to amorphous granular masses, invaded by glia-cells. In sections from the first dorsal segment (corresponding to the intrinsic muscle-groups of the hand) it is obvious that the cells of the anteromesial and posteromesial groups have undergone a marked diminution in numbers. Even more striking in this region is the wasting and shrinkage of the left anterior horn, which is paler than its fellow on the opposite side. This asymmetry of the ventral horns is seen in no other segment.

Nerve Fibres.—In Marchi sections, scattered through the white matter, are large numbers of fine blackened granules. They are particularly abundant in the root-entry zone, in the neighbourhood of the posteromesial septum, and in the marginal tracts. In the dorsal cord the fine dust-like particles are somewhat less numerous, and in the lumbar region this diminution is quite obvious.

Reich Corpuscles.—In the posterior columns of the cord, and to a less extent in the situation of the ventrolateral tracts, are large numbers of lilac-red granules; they are displayed in alcohol-fixed toluidin-blue and hæmatoxylin-eosin sections, appear to be lying free in the tissue spaces, and present no particular relationship to the vessels; in longitudinal sections they tend to be arranged in rows in the long axis of the cord, as though they were occupying the position of the degenerated myelin sheaths. From their morphological appearance there can be little doubt that they are the π -granules first described by Reich.

Axis-cylinders.—The majority are abnormal, showing tortuosity, localized swellings, and altered staining capacity. *Neuroglia.*—There is a considerable proliferation of glia-cells both in the white and grey matter; amoeboid glia-cells are present in the posterior columns. The investing pia mater has undergone a certain degree of thickening, but there is no evidence of cellular infiltration. The vessels of the cord are dilated, and hyaline thrombi are found in a few situations.

Spinal Nerve Roots.—In Marchi sections blackened droplets of altered myelin can be seen at more or less regular intervals in the long axes of individual fibres; their position corresponds with the constrictions or nodes of Ranvier.

REMARKS.

The histological appearances described above amply confirm the observation that, in fatal cases of gas poisoning, the brunt of the damage to the tissues falls on the central nervous system.

The diffuse widespread parenchymatous degeneration throughout the cerebrospinal axis is explicable on the hypothesis that there occurred an intense hæmatogenous intoxication; but at the same time we are left with the difficulty of understanding why particular areas of the nervous system—the cortex cerebri, the basal ganglia, and the cervical grey matter—were so much more severely damaged than other localities. There are few problems which offer greater difficulty than those concerned with the so-called selective action of toxins on the central nervous system, and while it is probable that certain of these are determined by a lymphogenous infection, it is obvious that in the case under consideration some other hypothesis must be advanced to assimilate all the aspects of the problem. Bearing in mind that in coal-gas poisoning carbon monoxide is carried in the blood, it is reasonable to suspect that the distribution of the lesions may be conditioned by certain anatomical peculiarities of the blood-vessels supplying the central nervous system. It will be convenient to consider separately the vascular arrangements in the cortex cerebri and basal ganglia.

The Cerebral Cortex.—Perhaps the most striking feature in the case was the zone of softening, limited with great fidelity to the deeper layers of the cortical grey matter. It is obvious that this morbid condition must have occurred in all situations at one and the same period of time, for the stage reached in the removal of the products of degeneration was everywhere the same. If the view that all the symptoms of carbon-monoxide poisoning are referable solely to a lessened oxygen-supply to the tissues be upheld, it is evident that the poorer the blood-supply to any particular area, the earlier and more severe will be the damage to that particular locality. It is therefore a matter of considerable interest to examine the arrangement of the cortical blood-supply with a view to determining the relative

vascularity of its different layers. On this point our knowledge is fairly definite. The investing pia mater supplies two types of vessel, one short and one long, both of which penetrate the grey matter. According to Bignami and Nazari the short vessels are purely cortical and terminate in a brush of fine arterioles in the deeper layers of the grey matter. The long vessels pass straight down to end in the centrum ovale, where each supplies a very narrow territory; anastomosis between these two types of vessel occurs in the deeper cortical laminae.

If the pial vessels are injected with a colouring agent, and a section of the cortical grey matter is examined under a low power, it is seen that the richest capillary network occurs in the infragranular layers—precisely the situation which exhibited such a widespread softening in this case. The areas with the most abundant blood-supply are those in which most damage was sustained, and it appears probable, therefore, that a mere deprivation of oxygen could hardly have conditioned this peculiar distribution of cortical necrosis. On the other hand, if it be assumed that carbon monoxide acts like other exogenous poisons, the infragranular layers with their fine arterial meshes would be particularly exposed to its noxious effects. Moreover, experimentally-produced anæmia of the cortex, by ligation of the vertebral and carotid vessels, shows that the small and medium pyramids are more affected than the cells in the deeper layers; the latter are, phylogenetically speaking, older and less liable to decay than are the more superficially-placed cells. The observation that an impoverished blood-supply leaves them relatively unaffected strengthens the view that an anoxæmia alone could not have produced the peculiar zone of softening seen in this case.

One other factor must be taken into consideration. The commonest cause of cortical softenings is unquestionably arrest of the circulation either by thrombosis or embolism, which is favoured in the grey matter by the anatomical arrangement and fine calibre of the venules and arterioles. Reference has already been made to the presence of cortical hyaline thrombi in all the situations submitted to microscopical examination, and although they occurred in numerous areas in which there was no trace of necrosis, it must be conceded that they played some part in determining the layer of intracortical softening. Their presence has been reported in other cases of carbon-monoxide poisoning in which punctiform hæmorrhages and softenings were present in the nervous system. In Mott's case the great majority of red blood-corpuscles showed a basophil reaction, which might be taken as an indication that the carbon monoxide had altered their physical properties in such a way as to favour thrombosis.

The evidence, therefore, is in favour of the view that carbon monoxide exerts its influence in two ways: indirectly, by altering the coagulative power of the blood, and diminishing the oxygen-supply to the tissues; and directly, by a specific action on the parenchymatous elements of the nervous system.

The Corpus Striatum.—One of the commonest and most interesting effects of carbon-monoxide poisoning is a softening of both lenticular nuclei. It has been recorded in a number of fatal cases, and appears to be even more characteristic than punctiform hæmorrhages. The lesion need not be a very large one, and, in fact, one must examine closely sometimes to find it.

It seems to be favoured by the peculiar vascular arrangement in this area. In 1898 Kolisko called attention to the existence of a special artery which is given off from the anterior cerebral, near its communicating branch. Though usually single, it is sometimes double, and runs upwards and backwards, supplying the caudate nucleus, part of the anterior limb of the internal capsule, and part of the external segment of the lenticular nucleus. Owing to its length and peculiar distribution, the blood that passes into it has to flow rather against the normal current, and when the general blood-pressure is very low, as in gas-poisoning, a tendency to stasis and thrombosis occurs. He regards its involvement on each side in cases of gas poisoning as the cause of the bilateral softening of the corpus striatum.

Even if Kolisko's views be accepted, any such anatomical explanation cannot be regarded as satisfactory, for other collections of grey matter in the immediate vicinity of the lenticular nucleus, which have practically the same blood-supply, are unaffected. In the case described above, no softenings were found in either the caudate nuclei or optic thalami, while in the globus pallidus lesions visible to the naked eye were found. Their appearance in areas immediately surrounding the vessels suggests that carbon monoxide has, in common with certain other poisons, a peculiar affinity for the tissues of the lenticular nucleus. While it is interesting to note that toxins in the general circulation are brought into closer relationship with the grey matter than with the white, it must be confessed that in the present state of our knowledge no adequate explanation can be given of the selective action of poisons on the nervous system.

Spinal Cord.—The morphological appearances in the spinal cord may be considered as indicative of a subacute hæmatogenous infection of the nervous system, and it is interesting to note that they tended to diminish in a caudal direction. The disappearance of nerve-cells and the wasting of the left anterior horn of grey matter in the first dorsal segment are in harmony with the clinical observations.

It will be remembered that on the third day of his illness the patient presented some wasting of the small muscles of the left hand, which was followed more than a fortnight later by a similar affection of the opposite hand; the more normal appearance of the right motor horn is explicable on the assumption that sufficient time had not elapsed for atrophy to become evident, although the individual nerve-cells had largely perished.

The numerous brilliantly-stained metachromatic granules found in sections which had been fixed and hardened in alcohol do not appear to have been previously noted in gas poisoning; they may be regarded as a catabolic product of the parenchymatous nerve-tissue.

Lastly, it is necessary to consider the reaction of the fixed connective-tissue cells in the cerebral hemispheres and brain stem.

It has been emphasized by Orr and Rows that the lesions in hæmatogenous intoxications are of a degenerative nature, and differ widely from those found in lymphogenous infection, in which the morbid phenomena of an inflammatory type reach their maximum. Although degenerative changes, very widespread in their distribution, were the most prominent feature in this case, the cellular proliferation in the adventitial sheaths of many of the vessels was undoubtedly of inflammatory nature. The possibility must therefore be entertained that some other morbid condition may have been present before the nervous tissue was exposed to the highly destructive action of coal gas. The presence of lymphocytes, plasma-cells, and rod-cells, the appearance of increased vascularity in the cortex, and the subacute decay of the ganglion-cells, are suggestive of a syphilitic infection. On the other hand, it must be noted that the brain showed no obvious cortical wasting, the microscopical features were evenly distributed throughout, and the ganglion-cells above the zone of softening preserved to a large extent their columnar arrangement. Moreover, a careful microscopical examination of the floor of the fourth ventricle did not reveal the presence of any ependymal granulations.

The altered chemical constitution of the cerebrospinal fluid was also suggestive of brain syphilis or dementia paralytica, but it would be surprising to find a normal fluid in gas poisoning associated with such profound degenerative changes in the nervous system. On the clinical side reference was made to an attack of mental depression which occurred in early middle life; the second attack appeared to be of a somewhat similar character, but with a more pronounced loss of the self-preservative instincts. There were no mental symptoms suggestive of general paralysis, and throughout the illness the pupils preserved their normal reaction to light.

On the whole the evidence does not favour the view that the patient was in the incipient stages of general paralysis, but the possi-

bility of a syphilitic infection cannot be entirely excluded. I shall therefore be content to leave this question undecided.

Finally, it may be stated that death in this case appeared to be due to heart failure, which may have been partly conditioned by the severe degeneration of the vagus nerves.

There can be little doubt that, had the patient survived, a profound degree of dementia would have supervened, for the intracortical zone of encephalomalacia was so widely distributed and so placed as almost to isolate the supragranular layers, which are thought to be concerned with the higher associations of intellectual life.

BIBLIOGRAPHY.

- DANA, "The Functions of the Corpora Striata", *Jour. Nerv. and Ment. Dis.*, 1908, 65.
 DAVIES, I. J., "Carbon-Monoxide Poisoning in the Senghenydd Explosion", *Brit. Med. Jour.*, 1914, July 11.
 GLAISTER and LOGAN, *Gas Poisoning in Mining and other Industries*.
 MOTT, "Carbon-monoxide and Nickel-carbonyl Poisoning", *Arch. of Neurol. and Psychiat.*, iii, 246.
 ORR and ROWS, "Lymphogenous Infection of the Central Nervous System", *Brain*, 1914, xxxvi, parts 3 and 4.
 BIGNAMI and NAZARI, quoted by Orr and Rows, *Jour. of Ment. Sci.*, 1918, Jan.