CASE III.—*Diplopia: Paresis of Accommodation: Congestion of Optic Disc: Lethargy: Delirium.*

Mr. K., aged 44 years. The history obtained was that, on February 21st, 1921, there was difficulty in reading and writing with diplopia. On February 24th he came to be tested for glasses because he found that he could read with his wife's glasses. He said he had been sleepy for the last few days. His condition was as follows: Vision: R. + 1 = 6.5 + 1.5 = J. 1 at 13 inches; L. + 1 = 6.5 partly + 1.5 = J. 1 at 13 inches. The irides were normal. The right disc of the fundi was slightly congested, the edge was sharp and there was a local swelling between the edge of the cup and the inner margin of the disc. The left disc was normal. There was diplopia, the images were uncrossed, on the same level, and separated by three degrees equal in all parts. There was paresis of divergence or spasm of convergence, but not paresis of a muscle. The subsequent history was communicated. The lethargy increased, with some delirium at night; there were involuntary tremors and general weakness, also slight paresis of one facial nerve. The temperature was 101° to 102° for five days. There was no albumin in the urine. On April 30th he had returned to business, but was still unable to read.

CASE IV.—*Diplopia: Paresis of Accommodation: Lethargy.*

Mrs. C., aged 36 years. On December 11th, 1920, she saw the tops of things double. This condition persisted for four days, but afterwards her sight was "unreliable"; she was giddy and also very shaky. She had some pain at the back of her left leg. On December 15th she was seen by her medical attendant, who found that the right pupil was larger than the left and that there was slight diplopia. On December 23rd the condition was as follows: Vision correction, R. 6/5 (6); L. 6/5 (3); the loss of accommodation R. + 1 D.; L. + 1.25 D. The irides: right pupil 3.5 mm., with very slight reaction to light and convergence; the left pupil was 2.5 mm., the reactions were normal. The diplopia was vertical, and confined to the lower right quadrant, the greatest in the lowest portion. There was paresis of the right inferior rectus. The knee-jerks were equal and exaggerated. She was pale and looked ill, but was not sleepy. Later on she became somewhat lethargic. On April 25th, 1921, she was well in all respects except that her eyes got tired after much reading, and the reactions of the right iris were sluggish.

In addition to these four cases the following may be mentioned:

CASE V.

A man, aged 52 years, seen during the later stages of recovery. There was a history of diplopia and difficulty in seeing in the earlier part of the illness. When seen there was no diplopia, and loss of accommodation was + 2.5, rather full for his age. The discs were redder than normal.

A household of four adults—husband, wife, child of 5 years, and lodger—was mentioned in a letter by the medical attendant of Case III. They were all sleepy, and each adult in turn accused the others of being cross-eyed. The lodger recovered without giving up his work as a bank clerk, although he sometimes fell asleep on his ledger, and had diplopia for all distances beyond 3 ft. from his eyes. This account of his diplopia suggests paresis of an external rectus. House groups have been described, but one consisting only of light cases must be rare.

Taking a general view, it will be seen that the cases are in the main miniatures, reproductions of severe cases on a reduced scale, rather than differing from these by the omission of certain symptoms.

Collecting the symptoms together from the various cases, the following points arise:

1. *Paresis of the ciliary muscle* is usually present, but is slight in degree and slightly different in the two eyes; from 1 D. to 1.5 D. being a usual amount. As the amount of manifest hypermetropia or presbyopia varies considerably in different patients under fairly similar conditions, it is not easy to state definitely the amount of paresis present; but in these cases the histories were fairly conclusive that there was paresis and that this was slight.

From the history it seems probable that the loss of accommodation was greatest very shortly after the onset, as was apparently the case with the diplopia, but no opportunity presented itself to verify this, for no case was seen earlier than the third day of the illness.

2. *Paresis of the iris* occurred in one eye of one case; it was of medium severity.

3. *Diplopia*.—This occurred in all the four cases given in detail, as well as in the five more casually mentioned. Three still had it when seen. Two of them had paresis of one muscle served by a branch of the third nerve, but Case II showed a relative convergence not due to paresis of a muscle, for it was equal in all positions. It is better to assume that the convergence was really due to weakened divergence than to spasm of convergence. The onset of

diplopia was sudden, but it became less severe after a few days, so that Case I thought it had gone when she visited me, though this was not so. When examined there was no obvious limitation of movement in the three cases; it required examination by a light and a red glass to demonstrate it, so that this symptom was in miniature.

4. *Optic Neuritis*.—In Case II it was distinctly retrobulbar, with diminished central vision and field and enlarged blind spot. In Case I it is mainly retrobulbar, but has come forward to the disc. But there is no projection above the surface, merely a filling up of the cup, the whole disc being white. The appearance of the vessels in the right eye as they emerged from this was quite unusual, as if they suddenly appeared out of plaster-of-Paris. Case III had a slight swelling in one part of the disc. Unfortunately the fields were not taken in this case. Case V had hyperaemia of the discs. His central vision was normal; circumstances prevented the taking of his fields. Thus, in these few cases, two had definite retrobulbar optic neuritis, and there was a suspicion that Case III and Case V had a slight degree of optic neuritis. As optic neuritis has not often been recorded, it may be accidental that so large a proportion of these present cases had it, as may happen with any special symptom in a small series; but it may be that this symptom is commoner than has been suspected, the state of the patients preventing the detailed examination necessary to establish the diagnosis of retrobulbar neuritis. Or perhaps optic neuritis may be frequent in the type of this disease existing in Devon. The few cases of optic neuritis recorded in France are summarized in *Archives d'Ophthalmologie*, 1920, pp. 423 and 429.

In regard to the geographical incidence, three of these cases occurred in Exeter, the remainder in North Devon. That these cases have come under the notice of an oculist raises the suspicion that there may be others, and that slight cases of this disease may be commoner than is at present thought.

It must be pointed out that the dominant symptoms in this group of cases—paresis of accommodation, diplopia, and sleepiness—are easy to recognize. To test the accommodation exactly may require special apparatus, but if a patient has difficulty in reading come on in two or three days, and this is associated with the other two symptoms, the practitioner will not go far wrong in assuming weakness of accommodation, and in establishing a *prima facie* case for encephalitis lethargica, notwithstanding the pitfalls which surround the subject.

A NOTE ON NEW GROWTH AND A REDUCING SUBSTANCE IN THE BLOOD.

BY

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THE theory that a factor was present in the blood which favoured the growth of certain bacteria was at one time commonly held, and was the basis of the old idea of a "diathesis," but when Ehrlich introduced his theories of immunity the older beliefs were mostly discarded and attempts to explain the incidence of disease have been greatly influenced by his teaching.

In common with several other pathologists, however, we have often felt that applications of Ehrlich's theory were limited and did not explain many of the phenomena of disease, and, while searching for further light on these problems of immunity, we tried at one time the effect of transplanting in succession each of the endocrine glands to see if any one of them by their secretions caused or accelerated the growth of tumours, and special interest attaches now to the fact that the only one that appeared to affect the growth of inoculated sarcoma in rats was the parotid.

The bacteria with filtrable spores which can be isolated from tumours have formed the subject of communications elsewhere. Finding that this class of bacteria only thrive well on media containing sugar, we examined the blood-sugar content of patients suffering from malignant disease and found the reducing substances invariably increased. (The picric acid method was used for testing the blood, hence we do not suggest that the figures given represent

only sugar, since other reducing substances may be included). Further, in most of the cases which have been under observation for any length of time a definite excretion of sugar in the urine (as tested by Nylander's fluid) has appeared from time to time. So consistent have been the results that we have recently felt able to rely on this test to differentiate between simple and malignant cases. For example:

1. A fluctuating swelling in the neck, possibly inflammatory, showed reducing substance 0.34 per cent., and proved to be sarcoma.

2. A case with long-continued gastric symptoms, possibly malignant, gave a normal sugar content, and on laparotomy showed only simple ulceration.

3. Two cases diagnosed as tubercle of the lung gave reducing substances 0.24 per cent. and 0.32 per cent. respectively. Both proved to be malignant, whereas other cases of phthisis gave a normal result.

4. A case of acute pain in the pelvis, without obvious cause, gave reducing substance 0.29 per cent., and *post mortem* an annular carcinoma of the rectum was found.

We do not wish at this stage to enter into any discussion as to the relations of the high percentage of reducing substance as cause, effect, or concomitant, but merely to relate that through finding it we were led to try the experiment of feeding rats on sugar after they had been injected with a bacillus with filtrable spores isolated from a case of human sarcoma. This sarcoma was of the melanotic type, but the pigment was scanty.

Injections were made into the tails of eight rats. Three of the animals were large enough for the emulsion to be injected into the tail vein, but in the five smaller rats the injection was subcutaneous. All external evidence of the injection had disappeared in a week, but after five weeks a nodule the size of a split pea was found at the point of injection in one of the small rats. This proved to be mainly a spindle-celled growth with a few giant cells, but some of the cells contained pigment.

One of the larger rats died after six weeks and showed extensive growths in both lungs. Microscopically large areas of necrosis were seen with a margin of cells some of which contained pigment. The original sporing bacillus was regained from this growth.

Two large rats remaining alive at the end of two months were killed and found to have nodules of growth in the lungs; one also had a primary nodule in the tail.

Six rats inoculated with the same culture, but not fed on sugar, showed no evidence of growth locally or in the lungs after three months. Six other rats fed on sugar, but not inoculated with bacteria, likewise remained healthy.

In view of the interest of the subject and the fact that rats are so difficult for us to obtain, we shall be pleased to supply a subculture of this bacillus to any cancer research institute that may care to repeat our experiments on a larger scale, and we should like to suggest to those working with simple inoculable overgrowths that they try the effect of feeding the inoculated animals on sugar.

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THE PATH OF TOXINS TO THE CENTRAL NERVOUS SYSTEM.

BY

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THE statement that the infection of the central nervous system probably takes place from the mucosa of the nasopharynx is frequently made, and an examination of the possible routes of such an agent, toxin or whatever it may be, would appear to be of interest as affording a possible explanation of the sequence of phenomena commonly observed.

Two possible routes present themselves: (a) By the blood stream, either directly or after lymphatic absorption; (b) along the nerves. A consideration of the facts would seem to indicate that both routes are made use of.

In the condition encephalitis lethargica we might suppose the toxin to work its way up the motor fibrillae of the facial nerve.

The path through the cribriform plate—in spite of the fact that the nasal lymphatics have been injected from the subdural space, and the short route offered by the nasal nerves as far as the meninges and olfactory nerves through

the meninges—is negatived by the fact that a toxin arriving in the anterior cerebral fossa could hardly manifest itself first by a lesion of nuclei in the tegmental region of the pons.

The facial nerve, supplying the buccinator and labial muscles in relation to the oral cavity, and probably the levator palati and musculus uvulae (lesser palatine branch of sphenopalatine ganglion, via vidian, and great superficial petrosal), in relation to the nasopharynx, could afford a mode of entrance. In the substance of the pons the ascending portion is in the closest relationship with the medial longitudinal bundle, and in all probability contributes fibres to that bundle. In addition it embraces the nucleus of the sixth nerve, in much the same manner that the loop end of a hairpin, bent on the flat, might hold a pea in its concavity.

The nucleus most intimately related to the medial longitudinal bundle is the oculo-motor, the cells of which are indeed divided by that bundle into several collections, which have been supposed to preside over separate orbital muscles. Whether the fibres for the orbicularis palpebrarum arise from the oculo-motor and descend to the facial in this bundle, as was supposed by Mendel, or whether they arise in a superior part of the facial nucleus, it is not difficult to believe that the most intimate connexion between the latter nucleus and the third is with that part of the third which presides over the levator palpebrae superioris. The trochlear and abducent nuclei are also, of course, closely placed to the same bundle.

What, then, are the symptoms we might expect from a toxin ascending by way of the facial fibrillae and medial longitudinal bundle? They are facial paralysis, ptosis, abducent or other ocular paralysis. In fact, the localizing signs commonly found in encephalitis lethargica.

MacNalty has suggested¹ that the stupor in this condition is occasioned by the cutting off of the afferent sensory stimuli, by involvement of the medial lemniscus, owing to its proximity to these medial somatic nuclei in the tegmental region.

I would submit that, in the region of the third nucleus, the medial lemniscus is pushed some distance laterally by the nucleus ruber; also that the lateral lemniscus, conveying auditory impressions, would not be involved; and that the lesions, though bilateral, are usually asymmetrical, so that one half of the sensory tract would probably be but slightly damaged. Therefore, one could hardly suppose that the afferent stimuli could be so entirely cut off as to produce the degree of lethargy observed. In fact, the type seen more approximates to that produced by drugs.

It would seem easier to explain it on the assumption that it was the general effect on the cerebrum of the toxin absorbed by the blood stream. There could hardly be doubt that toxin so absorbed would reach the cerebrum far more rapidly than it could travel up the nerves; but that it would be diluted by the total amount of blood in the circulation, come in contact with a greater amount of antibody, and would be supplied in equal amount to all the body cells. To suppose that, distributed in this way, it could pick out individual cranial nuclei would necessitate the assumption of a special affinity of certain motor cells for a particular toxin, and that such affinity was not possessed by other motor cells serially homologous and structurally identical—a hypothesis which does not commend itself.

Group 1, therefore, in which we have lethargy and asthenia but no localizing signs, might be supposed to be caused by absorption from the blood stream, in which death or recovery takes place before sufficient toxin has ascended by the nerve paths to cause such signs. The succeeding groups are those in which we have the effects of both in varying degrees.

The twelfth nucleus may be affected either by spread along its own fibrillae or from its connexion with the medial longitudinal bundle. Professor Marinesco, in the report quoted, expresses the opinion that the toxin travels by the way of the nerves. I have merely endeavoured to find an anatomical explanation for the sequence of events.

If we apply this hypothesis to the conditions met with in diphtheria, we have the causative organism living, and pouring out its toxin, on the walls of the pharynx and larynx, separated by a devitalized mucosa from muscles innervated by the cerebral part of the accessory (by way of branches of the vagus to the pharyngeal plexus). Toxins ascending along the fibrillae of these nerves would