Those of us who had to deal with malaria during the late war found a similar difficulty before us. But it was soon apparent to us all that, although we could treat primary malaria successfully by massive doses of quinine, such treatment was useless, if not harmful, in the chronic infections. Smaller doses were more efficacious. Syphilitic heart disease is of the chronic type.

Another consideration should also be borne in mind. It is well known that the administration of tuberculin in large doses to a patient suffering from phthisis may produce both a general reaction and a local one at the site of the focus. A similar reaction may occur in syphilis if large doses of the arsenical preparations are administered (Jarisch-Herxheimer reaction).¹⁹ The general opinion is that this is due to the sudden liberation of toxins from the bodies of the organisms that are destroyed. But, whatever the cause, it is obviously hazardous to expose a patient with, possibly, a narrowed coronary orifice to the danger of a local reaction and the complete obstruction of the artery. If arsenic is used in such cases it should only be subsequent to a course of mercury and iodide, and in moderate doses.

We have thus continued to treat cases of cardiac syphilis along the usual lines, with moderate doses of mercury and iodide, etc., over long periods of time. Small doses of kharsivan, or neokharsivan, are sometimes useful, as are Donovan's solution, the green iodide of mercury, arsenic iodide, and potassium iodide. The results which we have observed have sometimes been extremely satisfactory. We must always remember, however, that the true treatment of cardiac syphilis is preventive, the successful treatment of the primary illness, and that cardiac syphilis is the result of error, on the part of the patient or his medical adviser.

REFERENCES.

- ¹ Osler and Macrae: *Modern Medicine*, 1926, ii, 390.
- ² *Official History of the War: Diseases of the War*, 1923, ii.
- ³ Carey Coombs: *Lane Fox Lecture*, 1925, 3.
- ⁴ G. A. Allan: *Glasgow Med. Journ.*, August, 1924.
- ⁵ Robert Muir: *Textbook of Pathology*, 1929, 274.
- ⁶ Ambrose Paré, London, 1634, 287.
- ⁷ A. Lewer: *Army Medical Reports*, 1852, 512.
- ⁸ Inspector General Lawson: *Army Medical Reports*, 1868, app., 267.
- ⁹ F. H. Welch: *Diseases of the Heart among Soldiers*, 1870.
- ¹⁰ J. H. Wright: *Boston Med. and Surg. Journ.*, 1903.
- ¹¹ W. P. Herringham: *St. Bartholomew's Hospital Reports*, 1903, xxxix, 9.
- ¹² Allan Burns: *Observations on Some of the Most Important Diseases of the Heart*, Edin., 1809, 138.
- ¹³ J. A. MacWilliam: *British Medical Journal*, 1923, i, p. 51; ii, pp. 215, 278, and 1196.
- ¹⁴ C. S. Keefer and W. H. Resnik: *Arch. Int. Med.*, 1928, xli, 769.
- ¹⁵ H. Huchard: *Maladies du cœur*, 1839, ii, 54.
- ¹⁶ O. Josue: Quoted by Daniélopou, p. 111.
- ¹⁷ H. L. Heimann: *British Medical Journal*, 1927, i, 133.
- ¹⁸ D. Daniélopou: *L'Angine de poitrine*, Paris, 1927, 109.
- ¹⁹ J. H. Stokes: *Modern Clinical Syphilology*, Phil., 1926.

THE DIAGNOSIS OF FRONTAL TUMOURS.*

BY

JAMES COLLIER, M.D., F.R.C.P.,

CONSULTING PHYSICIAN AND EMERITUS LECTURER ON NEUROLOGY,
ST. GEORGE'S HOSPITAL, LONDON.

FROM the very nature of the cerebral hemispheres the regional diagnosis of disease situated therein is often a matter of peculiar difficulty. The cerebral hemispheres have their origin as appendages to the nervous mechanism subserving the olfactory sense, and have doubtless acquired dominance in the nervous system from the importance of the sense of smell in acquiring food and scenting danger, and so providing for the survival and advance of the race.

The cerebral hemispheres have no primary and direct connexions with any other function than that of smell, nor with any other region than the olfactory region. Secondary connexions are developed, as evolution proceeds, by mediate paths with every function and with every region of the body; and in the higher vertebrates the cerebral hemispheres become increasingly and more directly linked up with specific bodily functions, by the development of certain great white tracts which directly impinge upon, or take their origin from, the cerebral cortex. Interference with the integrity of these white tracts produces definite

and recognizable clinical signs. Even in man there are not many of these paths. There is the visual path entering the cortex of the cuneus and posterior pole. There is the auditory path to the temporal regions, the higher sensory path to the parietal lobes, and paths subserving incoming and outgoing speech connected with the left temporal lobe. With the knowledge of the anatomical details of these paths and of the results of lesions interrupting them, our knowledge of cerebral localization of function begins and ends. It is only because quick and easy compensation does not occur for lesions of these paths in man that we have even this slight knowledge of cerebral localization. In vertebrates lower than man such compensation occurs readily. Sherrington removed successively the right and left motor cortex from a chimpanzee. The animal recovered his motility perfectly. And when long recovered and a normal chimpanzee, an investigation was made to find where the motor cortex had been transferred to, and it was found that there was no excitable cortex—that there was no motor area in this perfect animal. No local motor function of the cortex had been abrogated by the destruction of the motor cortex. Only the pyramidal path had been destroyed, and Nature had found another way out for the exteriorization of motor function.

Hughlings Jackson, in the Croonian Lectures for 1884, formulated a theory of the way in which the nervous system worked. It has long since been proved to be anatomically acceptable by Golgi and his followers, who built up the "neurone" concept. It seems to be increasingly acceptable, physiologically and clinically, as time goes on. That part of Jackson's theory which concerns us on this subject may be put in two sentences. There are several structural and functional levels in the nervous system from the lowest to the highest. In the lowest level, which is represented by the spinal segment, simple structure and simple function are directly represented, but with each higher level everything below is re-represented in increasing compound proportion, so that in the highest level there can be no local representation, but a representation of some attribute of the physiological individual as a whole. Hughlings Jackson—so often on the lips of neurologists, so little read and so ill understood—is often called the "father of cortical localization," for his theory preceded Hitzig's experimental work; he was, in fact, the destroyer of cortical localization in that his theory is directly antagonistic to local residence of function in the highest part of the nervous system. Therefore, in considering what may be the signs of tumours within the frontal lobe, if we are to advance in knowledge we must divest our minds of any idea of local function, mental or other, peculiar to lesions of the prefrontal lobes; we must expect a varying clinical picture, and often one which is negative so far as localizing symptoms are concerned. We must bear in mind the great facility for compensation for local lesions within this region so fully emphasized by Gowers forty years ago, and keep in mind the disturbing effects of long-standing increase of intracranial pressure and of hydrocephalus upon the value of those signs which we use for localization, and strive to make a collect of those signs which have been useful to us collectively in the successful localization of tumours within the frontal lobe, for we do locate them successfully very often. I may conveniently divide the signs which are used for the location of a tumour within the prefrontal lobes into five categories:

1. The negative signs.
2. The contiguous signs.
3. The signs which have been deemed peculiar to, or especially marked in, prefrontal lesions.
4. The signs peculiar to lesions within the anterior fossa of the skull.
5. The signs revealed by ventriculography.

Negative Signs.

The negative signs are of especial importance, since tumours within the posterior fossa below the tentorium, and those of the occipital, parietal, central, and left temporal regions, except sometimes in their latest stages, give unmistakable signs of their position. Therefore if there be no definite localizing sign, it is commonly a matter of a

* A paper read in opening a discussion in the Section of Neurology and Psychological Medicine at the Annual Meeting of the British Medical Association, Manchester, 1928.

prefrontal or a right temporal site. It is only when a subtentorial tumour has given rise to hydrocephalus that we are likely to choose a frontal location from the mental reduction therewith associated—recently under my observation a syringomyeloma not larger than an inch of slate pencil, situated throughout the length of the aqueduct of Sylvius and not itself producing any local signs, gave rise to hydrocephalus and secondary dyspittuitarism closely simulating a suprasellar tumour—or when the long-raised pressure from a frontal tumour has shifted the brain stem backwards and pushed some of the cerebellum into the spinal canal and so caused paralysis of cranial nerves and cerebellar signs.

The Contiguous Signs.

The contiguous signs are those produced by the extension of some process connected with the growth—either pressure, oedema, or vascular disturbance—into the neighbouring ascending frontal convolution giving rise to motor weakness, or into the insula of the left side giving rise to interference with the execution of language, or into the paths converging to the forward part of the corpus callosum and so producing motor apraxia. The motor weakness is seen first and most in the face, rarely in the arm, and almost never in the leg. It is perhaps the most important lateralizing sign of a frontal tumour, but it does not distinguish a frontal tumour from a temporal tumour, which also frequently causes weakness of the face as a contiguous sign. When the facial weakness is obviously greater for emotional movement than for volitional the location should be a temporal one.

Difficulty in the exteriorization of language is a certain lateralizing sign of a left hemisphere lesion in a right-handed person, but it is also caused by tumours of the left insula and those of the anterior temporal region. It should be of the nature of a stammering defect or of a "pure aphasia" if due to a frontal lesion. The presence of any lack of speech acceptance or any difficulty of recall demands a location far back in the temporal lobe. Pure executive apraxia seems to be a certain sign of prefrontal involvement and to lateralize to the left side. Presumably it indicates a lesion extending deeply and far back in the upper two prefrontal convolutions. It can hardly be confused with agnostic or ideational apraxia, which results from a lesion further back in the hemisphere. Unfortunately it is of uncommon occurrence with prefrontal tumours.

Lesions Peculiar to the Frontal Lobe.

I will now proceed to a consideration of those signs which have been held to be peculiar to lesions of the frontal lobe, or to be especially marked as the result of such lesions.

Mental Symptoms.—We shall, I am sure, all agree that mental changes of a very variable order, from slight changes in the way of loss of reserve, childishness, and change of character, to severe disturbance such as megalomania, "witzelsucht," and amnesia, do result from tumours of the prefrontal region. I will ask you whether you agree with Cushing's very confident statement that mental changes are always much more conspicuous in left-sided lesions, for I am doubtful as to this point. On the other hand, we all know well that most extensive lesions of the frontal lobe often exist without any obvious mental change. The explanation seems to be the possibility of compensation, and whether the other frontal lobe is relatively intact as regards its callosal connexions, since bilateral frontal lesions always give rise, both experimentally and clinically, to marked mental reduction. The point of importance is whether mental changes are of sufficiently higher incidence with prefrontal lesions, as compared with lesions of other regions of the brain, as to make them reliable symptoms when other localizing symptoms are absent. "Seelenlahmung," or "soul paralysis," "witzelsucht," and "mind blindness," were all originally described as resulting from lesions of the posterior part of the hemisphere. The most dramatic mental changes that I have ever seen resulting from cerebral tumour occurred with tumours of the temporal lobe, the outer surface of the occipital lobe, and the splenium of the corpus callosum respectively. I wish especially to emphasize the early loss of memory and the mental reduction occurring in tumours

of the splenium callosi, because it may be the key to the explanation of mental changes and their variability in cases of cerebral tumour. I have in six cases made a correct regional diagnosis in the splenium callosi on the mental symptoms alone. Bristowe, many years ago, published four cases so alike as to enable him to make an accurate regional diagnosis in the last three of them. Giese and Bruns confirmed Bristowe's opinion, and Ferrier made an analysis of sixteen recorded cases and agreed with his clinical findings.

The lesion of the splenium callosi interrupts many of the connecting paths between the various regions of the hemispheres, and thereby, I submit, causes disorientation and mental changes. The isolated lesions of the brain which have been recorded as productive of "seelenlahmung," "witzelsucht," "mind blindness," and the apraxias have on my analysis always been lesions extending deeply into the white matter, and presumably freely interrupting transcortical paths, and I submit that it is the isolation of the various parts of the cortex from one another which is the chief cause of mental impairment rather than damage to the cortex itself. In Shilder's disease, for example, when the lesion is of the central white matter with the cortex intact, the mental change is very great. Therefore, in lesions of the prefrontal lobe, I suggest that mental changes are only conspicuous when the tumour extends deeply and cuts the callosal and other transcortical paths.

Frontal tremors, most marked upon the homolateral side and sometimes confined to that side, were first described by Grainger Stewart in 1906. Like other signs described at first as proper to the prefrontal lobe it has come to belong also to the temporal lobe, for Schwab in 1925, in 6 cases of temporal tumour, describes it as contralateral and of great lateralizing value. Kolodny, working under Gordon Holmes at Queen Square, describes it in 14 out of 38 cases of temporal tumour. In 4 cases it was homolateral, in 7 cases contralateral, and in 3 cases bilateral. He concludes that this tremor is not of lateralizing value, and that it will not distinguish frontal tumours from temporal tumours. Collins records an identical tremor in tumours of the post-central region. Recently, when called to a case of cerebral tumour in which the general symptoms were very urgent, these tremors were conspicuous in the left hand and foot, and they were the only localizing signs which I could find. Consequently an operation for left frontal tumour was carried out. On laying bare the bone for a very wide decompression a dark patch was seen in the posterior inferior temporal region, and this led to the completely successful removal of an endothelium buried in the back of the left temporal. How this tumour could have existed in such a situation in a right-handed subject without trace of speech defect or hemianopia, either before or after the operation, is a matter worthy of reflection. In this case Stewart's tremors were of certain lateralizing value, and the patient's life was saved thereby, though the location was wrong.

The "grasping and groping" reflex of Adie and Critchley is, as far as I know, a certain sign of prefrontal location which has not yet been seen with lesions elsewhere. Gordon Holmes thinks it is seen with very extensive frontal lesions, but I disagree with this opinion. Critchley associates it with lesions high up and far back in the prefrontal region.

Conjugate deviation of head and eyes, or of eyes alone, to the contralateral side, explained by an involvement of the frontal ocular area said to occupy Exner's region in the second frontal gyrus, has been repeatedly emphasized as of locating and lateralizing value, and recently by Gordon Holmes. Now I have seen Schafer's experiment producing conjugate deviation by stimulation of the occipital cortex. I know well of Ferrier's equally striking and similar result from stimulation of the parietal cortex, as well as Foerster's result from the temporal cortex, and everyone's result from the central cortex, and it seems to me certain that every cortical region must of necessity be an origin for incitations for conjugate deviation, considering the necessary association in life of conjugate deviation with every movement and sensation, and therefore conjugate deviation cannot be in any way special to the prefrontal lobes; nor do I believe that there is any special region

for this function. I have recently had under my care two patients with extreme and persistent conjugate deviation of head and eyes lasting for weeks. In one case a large glioma almost completely excavating the left frontal lobe, but not involving the cortex, was found. In the second case, in which the lesion was right-sided, the presence of complete hemianopia and astereognosis with marked hemianalgesia and very little hemiplegia made it certain that the lesion was in the posterior half of the hemisphere. I may, however, go so far as to say that conjugate deviation, when persisting in the absence of other localizing signs, may indicate either a frontal or a temporal location, but it will not distinguish between the two, for Kolodny found it well marked in 6 out of 38 cases of temporal tumour. When present it is of certain lateralizing value for tumours in any part of the hemisphere. It may be seen in the form of persistent deviation to the contralateral side, or of weakness and unwillingness in deviation to the ipsilateral side.

Loss or diminution of the trunk reflexes may be of great lateralizing value, and is said to be valuable in frontal location. But I hold that it is much more characteristic of the temporal tumour, and I have several times located a temporal tumour and had it successfully removed when this was the only localizing sign present. In one-half of Kolodny's temporal cases the trunk reflexes were completely absent on the contralateral side. The presence of these reflexes has no negating significance. In both frontal and temporal tumours it is probably a contiguous sign of pressure upon the pyramidal mechanism.

Incontinence is sometimes very marked in frontal tumours, even when the mental aberration is inconspicuous. I think I have seen it more often in temporal tumours. It was present in 20 per cent. of Kolodny's cases of temporal tumours.

Papilloedema was said by Leslie Paton to occur earlier and more severely with tumours of the hemisphere the farther forward these were situated. Recently Stopford has analysed another series of cases, and comes to the conclusion that the farther back the situation the earlier and more intense the papilloedema. I am inclined to agree with Stopford, though I do not think papilloedema is of any value, either in localization or in lateralization. Horsley affirmed that it was greater on the side of the tumour. With frontal tumours one might reasonably expect it to be less on the side of the tumour, since major local pressure at the back of the orbit tends to delay the onset of papilloedema. I have seen a good many very large frontal tumours come to autopsy without having developed papilloedema.

Lethargy of a deep but rousable kind has occurred many times in frontal tumour, and when existing without headache or papilloedema it has caused several cases at the National Hospital to reach the post-mortem room with the label "lethargic encephalitis." One patient came under my care with deep lethargy following immediately upon an attack of influenza. I cured this patient at St. George's Hospital with injections of collosol iodine and salicylates, and she remained quite well and at work until fifteen months later, when a second attack of lethargy proved fatal, and I found a very large right-sided frontal tumour. This patient had no headache and never developed papilloedema. I am well aware of lethargy as occurring with pineal tumours and tumours of the upper brain stem, but I have only seen lethargy of this nature in tumours of the frontal region so far as the hemispheres are concerned.

Fits of many kinds occur with frontal tumours. I have seen characteristic minor attacks occurring frequently as the sole epileptic manifestation. Hughlings Jackson spoke of convulsions with bilateral commencement as indications of frontal location, but perhaps this was more from theoretical considerations than from practical experience. The convulsions I have seen have always commenced with conjugate deviation, which deviation has been a sure lateralizing sign. Status epilepticus is an interesting frontal symptom. I have records of two cases which were in hospital under treatment for fits, and in which no signs of local lesion of the nervous system were found. These patients developed status epilepticus and perished, and in

both cases a frontal tumour was found. I have no knowledge of any other region of the brain in which a tumour has produced status epilepticus.

There remain for consideration certain phenomena, such as Mayer's reflex, Leri's reflex, and Hoffman's reflex, which are said to be absent in prefrontal lesions, and Wessenberg's sign, which is supposed to be found only when a prefrontal lesion is present. Of these signs I have not much experience.

Signs Peculiar to Lesions of the Anterior Fossa.

The signs peculiar to the anterior fossa of the skull are those of pressure upon the olfactory tract, the optic nerve or chiasma, or upon the nerves and vessels passing through the sphenoidal fissure, and those of bony involvement. These are always certain localizing and lateralizing signs, but they only obtain with a hard tumour coming to the surface of the orbital lobe or with a growth of meninges or bone.

Signs Revealed by Ventriculography.

There remains the method of ventriculography, which in skilled hands has resulted in many brilliant successes in this and in other difficult regions of the brain.

I hope that in introducing this subject to you I have said nothing that is dogmatic and nothing that is antagonistic to the feelings of any of you. If I have done so my fate will surely be that of all who are too sure about so delicate a subject as location within the cerebral hemispheres. May I tell you a story of one who did dogmatize? It concerns no less an observer and fine neurologist than Albert Knapp, who, in his monograph on *Tumours of the Temporal Lobe*, wrote: "Paralysis of the sixth nerve, so common in tumours of the hemispheres elsewhere, is practically unknown with temporal tumours, and its absence is of localizing value. I have myself recorded the only case in the literature of the subject." I am informed that after publishing this monograph the six consecutive cases of temporal tumour which came under Professor Knapp's care all had sixth nerve paralysis.

INCIDENCE OF DISEASE OF THE BLADDER IN WORKERS IN CERTAIN CHEMICALS.*

BY

THOS. H. WIGNALL, M.B., B.Ch.,

APPOINTED SURGEON, HOME OFFICE, TO BRITISH DYESTUFFS
CORPORATION, LTD.

I HAVE lived in the vicinity of a chemical works for nearly thirty years, and for the period 1900 to 1910 had, as patients, many men who had worked at this factory for several years. Since 1918 I have held the position of appointed surgeon for the factory, and have had, at all times, perfect freedom of access and much help from the managers and staff chemists in all problems that arose.

In the early periods (1860 and on) of the making of certain dyes from coal-tar products arsenic was largely used (As_2O_3); workers were not protected in any way, and cases of toxæmia were only beginning to be observed. At these times any man who offered himself got a job, if such were available. Cases were sent to the doctor simply as they happened, and no records were kept. No other system was thought necessary. Now we only take mature men below a certain age; they are examined as to indications of good health and evidences of skin trouble. A well-fitted first-aid station and a competent nurse are provided, and all cases are seen medically on the spot as soon as possible after report. Also, men are encouraged to report on any deviation from general health, and such cases are investigated, there being an attempt to promote good feeling always between doctor, nurse, and men, so no trivial report is ignored, and all cases are recorded. It is, however, not easy to give percentages of incidence of disease in chemical workers, because usually a man's job is not the same over a long period, and prior to coming

* Read in opening a discussion in the Section of Occupational Diseases at the Annual Meeting of the British Medical Association, Manchester, 1928.