THE WERNICKE SYNDROME

With Special Reference to Manic Syndromes Associated with Hypothalamic Lesions

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The following study is based upon five complete cases of Wernicke's syndrome. In only one case was there a history of alcoholism; two of the subjects suffered from pernicous anaemia; one gave a history of hyperemesis gravidarum, and the last of gastric carcinoma. In two further cases, the one of alcoholism and the other of pernicous anaemia, no complete investigation could be carried out; it is known, however, that both these patients had Korsakow's psychosis and in both the mammillary bodies were found to be severely affected.

The occurrence of the Wernicke Syndrome in all these conditions is now a recognized fact (Neuburger, 1937; Campbell and Biggart, 1939; Sheehan, 1939; Sinclair, 1939; and others). It has also been well established that the common etiological link is a deficiency in thiamine. Alexander (1939, 1940) was able to produce lesions comparable with those of the Wernicke Syndrome in pigeons fed on thamine-free diet rich in other food-stuffs and containing in excess the vitamins A, the remaining Bs, C, and D. Alexander's results were in accordance with those of Prickett (1934) and Zimmerman (1939/40, 1940), and have since been amplified by similar findings in foxes (Alexander, Green, Evans and Wolf, 1941; Evans, Carlson and Green, 1942) and in cats (Ferraro and Roizin, 1941).

In this paper it is not proposed to describe the pathology of all the cases in detail; this would mean much repetition of findings which have been studied previously. Only one case will be given in full, as it was atypical both clinically and pathologically. The rest of the material will be utilized for comparison and also for the description of certain unusual features which have not been dealt with adequately in previous publications.

Case report *

William H. G., aet. 62, admitted to Cane Hill Hospital on 19th August, 1941. (The following report is by Dr. Lilly, Medical Superintendent.)

Family History: The only abnormality known is that his sister is an inmate of Bexley Hospital. The Medical Superintendent, Dr. L. C. Cook, kindly supplied the following information about her. She was admitted in 1930 in a very apprehensive, agitated state which soon cleared up, leaving her a simple but stable type of feeble-minded woman, lacking confidence, and incapable of finding for herself independently. She reached standard II at school, but can just read and write. She tells me she got very depressed after her mother died during the last war, but did not have to go to Hospital. I can find no other history of Manic-depressive tendency."

Personal History: Nothing is known of any physical or mental abnormality until the patient's present disease. In March, 1941, he was an out-patient at Charing Cross Hospital suffering from inoperable gastric carcinoma and was sent home to the care of his wife. His psychotic condition commenced at the beginning of July, 1941, when he became elated, giving way expensive presents, and, and, when remonstrated with by his wife, "flew into a rage," making it impossible for her to take care of him. During the time in St. Francis' Hospital, to which he was admitted on account of his psychotic condition, he was over-active and interfering, and refused to conform with ward discipline, becoming excited, noisy and abusive when efforts were made to restrain his activities.

On admission to Cane Hill Hospital he was in very poor health and was emaciated. He was found to have a hard palpable mass in the epigastrum beneath the left costal margin. Otherwise, except for some external hemorrhoids, no noteworthy physical signs of disease were discovered. The blood Wassermann and M.K. reactions were negative. His physical condition steadily deteriorated and he vomited occasionally and lost weight. His feet became oedematous and from 10th January, 1942, the oedema increased rapidly until his death on January 20th.

Mental Condition: On admission he appeared elated, garrulous, rambling, and grandiose, expressing a variety of delusions, such as, that he was wealthy and talented, and could achieve great things if his family were not bent on thwarting him. He would have been a great success as an actor if he had been allowed to go on the stage, or as a bishop if he had gone in for the church; he offered to give the Medical Superintendent £1,000 if he needed the money. He was oriented as to time, space, and his own personality, although he completely lacked insight into his conduct. At this time there were no signs of confusion. The diagnosis, as stated in a certificate forwarded to the Board of Control, was: "Attack of mania."

During the period between 19th to 25th August, his emotional state remained much the same, although on two occasions for a short time it changed into one of misery during which he made no effort to answer questions, being mute and inaccessible. On September 2nd he was still elated, showing flight of ideas and grandiose delusions. He was often unsociable with the other patients and still lacked insight. Towards the end of September short periods of confusion occurred for the first time, although they did not really affect his generally manic condition. They increased somewhat in frequency and duration during October, when he appeared to be hallucinated at times and also to be deteriorating intellectually. During December confusion and memory defects progressively dominated the mental picture, although he remained elated apart from occasional depressed phases. In the last days of his life, when his

* This case has been briefly demonstrated and discussed at a meeting of the Psychiatric Section of the Royal Society of Medicine on 15th February, 1944.
physical condition progressively failed, he became somnolent and died on 20th January in a state of coma. Nothing was noted in his case history about disturbances of water and carbohydrate metabolism or of temperature regulation.

The autopsy confirmed the diagnosis of carcinoma of the stomach. The brain was sent to the Central nucleus. Fig. 1 and 2 show considerable gliosis Pathological Laboratory for histological investigation.

Macroscopic inspection of brain.—Weight 1,500 gr. after relatively short fixation in formalin. Convolutional pattern well preserved. Considerable thickening of leptomeninges at the base of the brain, particularly within the interpeduncular space. The basilar arteries showed some thickening of walls and rigidity, but no atheroma. On coronal dissection of the cerebrum nothing abnormal was seen except small cribrules in parts of the white matter, The hypothalamus was not cut, but embedded as a whole in celloidin. All parts of the cerebellum presented a peculiar appearance. There was no genera reduction in size, but a glassy appearance was noticed in what would correspond to the granular layer. While in normal specimens only cortex and white matter of the lobules are distinguishable, in this case, thus, three conspicuous layers were noticed.

Histological investigation

Hypothalamus.—Slight changes were seen in the nuclei of the parolfactory region including the nucleus of the diagonal band. These consisted of patchy glial and mesodermal proliferation leading to some degree of cortical disorganization and unspecific degenerative changes in the nerve cells. The main lesion began, however, at a slightly more caudal level, at the rostral end of the paraventricular and vascular proliferation around the optic recess and the anterior tip of the 3rd ventricle. Part of the ventricle in this plane is without ependymal lining, but trabeculi of mesodermal tissue are seen traversing the cavity. The unusual separation of the optic recess and the rest of the 3rd ventricle by a band of gliol tissue is due (as was kindly confirmed by Prof. le Gros Clark) to the oblique direction of the original cut. The rostral end of the paraventricular nucleus is heavily involved in the glio-mesodermal reaction, most of its nerve cells showing definite signs of severe degeneration, although their characteristic appearance is still recognizable with higher magnification. The same applies to the rostral end of the supraoptic nucleus (Fig. 2) and the medial and lateral preoptic area.

The chiasma itself shows marked gliosis and vascular proliferation in its dorsal and dorsolateral aspect (Fig. 2). The gliosis extends around the optic recess and becomes very marked in the region of the supraoptic nucleus. No calcification of blood vessels is seen at this level. In addition to these more chronic lesions, areas of recent "paling" with focal outfall of cells or cell "shadow" formations are occasionally seen, but typical ischemic or homogenizing cell degeneration have not been found.

If one proceeds in serial sections further backwards changes are seen in almost every hypothalamic centre. Nowhere, however, do they approach the extent of the anteriorly located lesions described above. The most constant and very unusual finding is calcification of small and medium-sized blood vessels (Fig. 3). This is seen in the dorso-medial ventro-medial, and supraoptic nuclei, in and near the paraventricular nuclei, tuberal nuclei, chiasma and optic tracts, median eminence, fornices and, occasionally, in other subependymal parts of the 3rd and lateral ventricles. The cellular configuration at the level of the posterior part of the
supraoptic and the tuberal portion of the hypothalamus is much less affected than the anterior portion. Note, for instance, the approximately normal appearance of the tuberal region (Fig. 4). Many of the nerve cells, however, show moderate degenerative changes, but rarely severe and ischemic changes. Fig. 4 shows some focal reduction within the supraoptic nucleus at the tuberal level, together with some excess of glial and vascular proliferation noticeable under high magnification.

The caudal or mamillary portion of the hypothalamus is least affected. The lateral hypothalamic nucleus and its condensation of large cells called by some writers mamillo-infundibular nucleus is almost free from change. The mamillary body gives in Nissl stained sections a pale appearance both in the medial and lateral (nucleus intercalatus of several authors) nuclei (Fig. 5). High-power examination reveals degeneration of nerve cells, a proportion of which show various stages of ischemic change. There is very fine and recent glial fibrosis throughout the centre, but only an abortive proliferation of vessel wall elements. No calcification of vessels is seen, nor, in myelin preparations, any degeneration of the mamillo-thalamic tract.

Fig. 4.—Nissl stain, × 6. Hypothalamus, tuberal portion.

The pia-arachnoid membrane in the interpeduncular space was considerably thickened, as was already noticed on macroscopic inspection. This showed most conspicuously in Van Gieson preparations where the recent increase of collagen containing fibrous tissue stained a bright red colour. The vessel walls were fibrosed; only occasionally were early atheromatous changes seen. The fibrous tissue in and around the infundibular stalk and also between the latter and the chiasma showed recent proliferation.

Brain Stem.—There were changes in the quadrigeminal region and in the inferior olives. Early gliomesodermal proliferation was seen in the grey matter around the aqueduct and within the posterior colliculi. Nerve cell changes of the acute, severe, and occasionally ischemic type were seen. Occa-

Fig. 5.—Nissl stain, × 26. Mammillary body.

sionally diseased nerve cells recalled the appearance of gemistocytic glial cells. Stern (1933) has pointed out that this change is peculiar to this region and may denote an interference with the blood supply. In parenthesis, it may be mentioned that apparently similar nerve cell changes have been seen in the mamillary body by Neubuerger (1931) and Bodchetel and Gagel (1931).

The changes in the inferior olives will be described and discussed in a later section of this paper.

Cerebellum.—In Nissl preparations the Purkinje cell layer stands out distinctly owing to a failure of the granule cell layer to stain with basic dyes (Fig. 6). With high-power magnification it was seen that many of the granule cells had disappeared while others stained faintly as shadows or clumps...
of granular debris indicating advanced degeneration. In other places the remaining granule cells seemed to be swollen and displayed the tendency of clustering together which has been aptly called conglutination. The Purkinje cells were also diminished in number, a few exhibited various forms of degeneration, but both ischemic and homogenizing changes were absent. The Bergmann glial cells were considerably increased in number and showed signs of recent activity, but nowhere was the characteristic shrub-like appearance of proliferated microglia seen in the molecular layer.

Myelin preparations revealed poverty of fibres in the granule layer, and also some slight diffuse or patchy reduction in the white matter of the lobules. More fibres were seen within the granular layer after Bielschowsky impregnation which showed the normal formation of baskets, a few of which appeared to be empty. The Bergmann glia cells contained excess of lipoids. Much fat was also seen in glia cells and in mesodermal elements of the granule cell layer and, to a lesser degree, of the white matter. Impregnation for microglia did not demonstrate any appreciable proliferation nor was there much fibrous gliosis in Holzer preparations except in the white matter which contained some areas of patchy astrocytic proliferation. The dentate nuclei was little affected apart from excess of lipofuscin in nerve cells and some degree of patchy glial proliferation.

Cerebral Hemispheres.—The most striking change was a moderate fibrosis of blood vessels in the meninges as well as in the brain. In the white matter a definite rarefaction of the issue in close vicinity to the thickened vessels has produced the picture of small “cribri.” An accumulation of corpora amylacea was often seen. No appreciable outfall of cortical nerve cells was noted, nor was there any certain increase of glial cells. The lipoids in neurones, glial cells and vessel wall elements corresponded in amount to the age of the patient. Neither neurofibril change nor senile plaques were observed after Bielschowsky staining. No noteworthy change, apart from subependymal calcification of blood vessels already reported, was seen in the striate body, globus pallidus, thalamus, and the remaining centres of the basal ganglia.

DISCUSSION

Diagnosis

There is little doubt that the case, despite some unusual features, is one of Wernicke’s syndrome. The development, in the course of a severe gastric disease, of mental symptoms, characterized by confusion, hallucinations, and memory defect, and terminating in coma and death, combined with the pathological finding of a lesion in the hypothalamic area, puts the diagnosis of Wernicke syndrome on a solid basis. Clinically the psychosis was atypical, and the significance of its unusual features in relation to the pathology will be discussed in a later section. The unusual pathological features include the prevalence of advanced lesions in the anterior part of the hypothalamus and degeneration resulting in calcification rather than proliferation of blood vessels. The present writer has been unable to trace any previous report in the literature of calcification of hypothalamic blood vessels in cases of Wernicke’s disease. It is interesting to note that Campbell and Biggart (1939) included the optic nerves among the vulnerable structures in the Wernicke syndrome.

The lesion in their case 11, was, however, in the nature of softening, whereas in the case described in this paper, gliosis and abundant calcification of blood vessels in the optic tracts was noted. Much calcification was found in the subependymal regions of the 3rd and lateral ventricles and the median eminence. There was no calcification in the caudal (mamillary) part of the hypothalamus; the mamillary body was seen undergoing ischemic nerve cell degeneration without vascular proliferation. Such absence of the vascular proliferation has been occasionally noted before (Neubuerger, 1931).

In only one of my five cases was there a slight late involvement of the quadrigeminal region, and in no case were the vestibular and vagal nuclei affected. These centres are known to be susceptible in Wernicke’s syndrome. The lesions in the cerebellum and inferior olives and their significance will be the subject of separate paragraphs.

It is worth mentioning that the nerve cell change known as primary irritation, which is so prominent in pellagra, has not been seen in any of my cases, nor have manifestations of Wernicke’s syndrome been encountered in my pellagra material. This interesting and surprising mutual exclusiveness will be the subject of a separate paper.

The manic syndrome in lesions of the hypothalamus

The psychotic manifestations associated with the Wernicke syndrome are usually of the confusional type which when becoming chronic passes over into a typical Korsakow’s psychosis. Many authors believe that the affection of the mamillary body is invariably associated with Korsakow’s psychosis (Kant, 1932/33). In our material, confusional states, Korsakow syndrome, somnolence and coma

Fig. 6.—Nissl stain, ×12. Cerebellum. Note disappearance of the granular cells.
dominate the psychiatric picture with the exception of the one case which has been described in full and in which also the localization of the lesion within the hypothalamic area appeared to be significantly different. In the case, described in detail in this paper, the psychosis presented for three months (July–September, 1941) all the characteristics of a manic syndrome with only two short intervals of depression. From the end of September onwards confusion, hallucinations, memory defect and intellectual deterioration gradually supervened, slightly at first, and slowly increasing until in January, 1942, the patient became somnolent and died in coma.

The incidence of manic syndromes and rage-like excitement in hypothalamic lesions has been recently discussed (cf. reviews by Grinker, 1939; Ranson and Magoun, 1939; Alpers, 1940; Kennedy, 1940). In brief, the experimental and pathological evidence so far available is as follows:

Bard (1928) produced sham rage in cats whose cortex and cranial half of the hypothalamus had been ablated. These outbursts of rage resembled the behaviour of the infuriated normal animal and were not comparable with the pseudoaffective reflexes obtained in cats after section of the midbrain. According to the author the mechanism responsible for sham rage lies within an area comprising the caudal half of the hypothalamus and, possibly, the most ventral and caudal fraction of the corresponding segment of the thalamus. Fulton and Ingraham (1929) placed lesions in cats anteriorly to the chiasma. They believed that the rage reaction produced in three out of four cats was due to division of the hypothalamic tracts. In this regard some more detailed information has been given by Spiegel, Miller, and Oppenheimer (1940). They experimented on cats and dogs with a view to studying those parts of the forebrain which send impulses to the hypothalamus. Lesions of the frontal pole merely produced hypermotility, whereas definite manifestations of rage appeared if the lesions involved the olfactory tubercles. Destruction of the olfactory bulbs and their stalks had only slight and transitory effect. These authors were also able to produce rage after bilateral lesion of the amygdaloid nuclei and the hippocampus-fornix system. In the discussion which followed the paper Papez (1940) reported the production of drowsiness and twilight states in cats by removal of the anterior portion of the cingular gyrus. The work of Klüver and Bucy (1939) was also mentioned; they failed to produce rage in monkeys after bilateral ablation of the temporal lobes. They observed, however, an absence of emotional reaction if the temporal tissue which had been removed contained the hippocampal region. Ranson and his collaborators were primarily interested in the production of somnolence and catalepsy (Ranson and Ingram, 1932; Ranson, 1939; Ranson and Magoun, 1939). Bilateral lesions in the lateral hypothalamic areas extending to the caudal border of the mamillary bodies were most effective in producing somnolence, while catalepsy followed if the lesion damaged the ventral part of the brain stem from the posterior part of the hypothalamus to the 3rd nerve. If, however, the lesions were placed more anteriorly in the lateral hypothalamus, as was done in six monkeys, the animals were only temporarily drowsy and then became increasingly wild. In none of these six animals were the mamillothalamic tracts, mamillary nuclei, posterior hypothalamic nuclei, or the posterior part of the lateral hypothalamic area involved. Ranson and Magoun (1939) conclude, in agreement with Bard (1928), that a mechanism is located in the posterior part of the lateral hypothalamus which when activated excites the entire organism. Maniacal excitement has also been seen after very small lesions in the grey matter around the aqueduct in the plane of the midbrain. (Foerster and Gagel, 1933/34; Bailey and Davies, 1942.)

In man Foerster and Gagel (1933/34) were able to make important observations of an experimental nature during operations at the base of the brain. Temporary manic excitement occurred if the slight pressure of a swab was applied to the chiasmatic part of the hypothalamus. This was observed in four cases, and it was expressly stated that from no other position could a similar condition be elicited. Whether the manipulation was in the nature of a stimulus (as the authors believed) or that of a slight depression of normal function of this region, is, however, uncertain, but the experimental results described above would favour depression of function.

Manic syndromes supposed to be due to lesions within or near the hypothalamic area have been described in human pathological material by a number of workers (Schuster, 1902; Fulton and Bailey, 1929; Cushing, 1929; Urechia, 1934; Cox, 1937; Dott, 1938; Alpers, 1940; Vonderah, 1940; Stern and Dancey, 1942). In most of these recorded cases the lesion was a tumour or a cyst, and precise localization was thus difficult if not impossible. Guttman and Hermann (1932), who are widely quoted in this connection, were dealing with confusional states (“amnisti psychosen”). But their work is important in a negative sense, for they found that a lesion between the hypophysial stalk and the anterior border of the pons—that is to say, in the caudal part of the hypothalamus—is responsible for this type of confusional psychosis. Cases and syndromes described by Schilder and Weissmann (1927), van Bogaert (1927), and L’hermitte, Levy and Treles (1932), obviously belong to the same category. This apparently applies also to the case of akinetic mutism published by Oldfield, Cairns, Pennybacker and Whitteridge (1941), in which there was a cyst of the 3rd ventricle and to two cases showing traumatic stupor described by Jefferson (1944), in both of which the cerebral hemispheres and the anterior half of the hypothalamus were, significantly, found to be normal. The contributions to the problem made by Kleist (1934) cannot be dealt with in detail, as his book was not accessible to the present writer. In a subsequent paper, however, Kleist (1937) states that
excitement may be produced by frontal lesions involving the anterior part of the diencephalon and hypothalamus, whereas general depression of function and stupor is caused by temporal, parietal, or occipital lesions involving (directly or by pressure) the posterior part of the diencephalon. The criticism has been made against Kleist that his views are based mainly on macroscopic investigations.

My own case is not only in agreement with the results of previous experimental investigation, but shows the essential clinico-pathological relationship with greater clarity than any of the human cases previously reported in association with the manic syndrome. In this case of atypical Wernicke's syndrome in which a manic syndrome prevailed for three to four months of a total psychotic period of six months, it is seen that, contrary to the usual pathological findings, the more severe lesions were placed in the anterior (supraoptic) portion of the hypothalamus. Fig. 7 indicates the striking similarity of the localization of the lesion in our case with those produced experimentally by Fulton and Ingraham (1929) and Ranson and his school (cf. Ranson and Magoun, 1939). The possible objection that the Wernicke syndrome is a rather acute condition lasting as a rule for not longer than a few weeks can be met by the fact that the histological lesions are unusually chronic in appearance as exemplified by the heavy fibrous gliosis and extensive calcification of small blood vessels. Moreover, there may have been preceding the histologically visible lesion a local metabolic effect arising from the thiamine deficiency and setting up what is now often referred to as a biochemical lesion.

In recording this case as a human counterpart to experimentally produced rage it is impossible to over emphasize the extraordinarily complex and controversial nature of the problem. In the discussion following Kleist's (1937) paper, it was said that attempts to localize psychological function (apart from the gross loss seen in dementia) will always remain in the "anteroom of the mind." Whether or not this general statement is true it is, in substance at least, in line with much recent criticism directed against attempts to regard the hypothalamus as a centre of emotion, personality make-up, consciousness and other vital mental processes (Kleitman, 1939; Grinker, 1939; Alpers, 1940; Masserman, 1942, 1943; Jefferson, 1944). On the strength of personal and other experimental work Masserman emphatically rejects all theories which postulate a localization of emotional experience in the hypothalamus, whose only established rôle is to reinforce and co-ordinate the neural and hormonal mechanisms of emotional expression. According to this author emotion is a "highly integrated conative, cognitive, and affective somatic reaction in which not only the central nervous system but the entire organism functions as a psychobiologic whole."

It is therefore imperative to consider hypothalamic function and dysfunction in its wider anatomical and physiological implications. Several connections with the frontal cortex have been either established or are likely to exist (1) Prefrontal cortex—dorsomedial thalamic nucleus—periventricular fibre system passing to the posterior hypothalamic area; (2) frontal cortex—septal nuclei—septo-hypothalamic tract; (3) frontal cortex—zone incerta—mamillary region; (4) parolfactory cortex—medial forebrain bundle—hypothalamus. The mamillary body is connected with the anterior part of the cingular cortex via the mamillo-thalamic tract and anterior thalamic nucleus, and with the pyramidal cells of the Ammon's horn via the fornix system. Lastly the hypothalamus maintains important connections with caudal centres in the brainstem and with the pituitary gland. Many of the centres linked with the hypothalamus are part of the diencephalon, but it is unlikely that all are concerned with olfactory function. The Ammon's horn and anterior cingular gyrus (anterior limbic region) are more highly differentiated in man than in any of the lower mammals (Rose, 1935). The gyrus cinguli has been considered to be the cortical representation of the vegetative nervous system by Economo and Koskinas as long ago as 1925 (quoted from Rose, 1935).

It is interesting, in the light of these observations, that Papez (1937, 1940) regards the hypothalamus, parolfactory region, amygdaloid nuclei, anterior thalamic nuclei, cingular cortex, and the hippocampus as members of a "well interconnected and harmonious mechanism which may elaborate the functions of central emotion as well as participate in emotional expression." Obviously, this concept refers to conditions in animal brains; in fact, in its present form, it was outlined by the author in the discussion which followed a report on their experimental work by Spiegel, Miller and Oppenheimer (1940, loc. cit.). In Kleist's (1934, 1937) scheme which is based on human experiences, various regions in the frontal lobe combine with the cingular gyrus and hypothalamic and thalamic levels to form the structural basis of personality organization. His views have been hotly disputed, particularly on the grounds of his rigid dogmatism, but it cannot be denied that most of the theories

**Fig. 7.**—Diagram reproduced after modification from Le Gros Clark (The Hypothalamus, Oliver and Boyd, Edinburgh). The dotted lines indicate approximately the extent of the severe lesion.
A. MEYER

which have been recently developed to explain the mechanism of prefrontal leukotomy are based on similar conceptions.

Electrophysiological evidence seems to support the interrelationship of the hypothalamus with other regions of the brain. Measuring thermal relations by means of thermo-electric couples, Serota (1939) found increase of heat in the hypothalamic area after induction of emotion such as fear, rage, or anticipation of food. It has been shown that electrical stimulation of the hypothalamus (in animals and man) may result in massive cortical discharges (Grinker and Serota, 1938; Ranson and Magoun, 1939), whereas destruction abolishes all cortical activity (Grinker and Serota, 1938; Obrador, 1943). Although these results require confirmation, it can be confidently expected that electroencephalography will play a major part in the further elucidation of these problems.

This close inter-relationship may, perhaps, explain why a lesion in or near the hypothalamic area might break up complex patterns of emotional behaviour, although the hypothalamus itself is solely concerned with emotional expression. A lesion placed at or in front of the rostral portion of the hypothalamus would be particularly likely to disrupt frontohypothalamic connections. Phylogenetic differentiation tending to increase frontal preponderance may possibly account for some of the differences between manic syndromes in man and the primitive rage reactions of experimental animals.

In view of the difficulty of a satisfactory explanation some workers (Riddoch, 1938; Stern and Dancey, 1942) have postulated a constitutional factor in addition to the affection of the hypothalamus. This is in keeping with the popular assumption that an intrinsic factor is in operation whenever symptoms of an endogenous psychosis—mania, depression, schizophrenia—occur in the course of an organic disease of the brain. In the case investigated by Stern and Dancey (1942) positive hereditary evidence was available. The only constitutional taint in our case is that the sister of the patient is a mental defective inclined to occasional depressions of an apparently reactive type. The acceptance of a hereditary determination need not necessarily invalidate the pathogenic significance of the hypothalamic lesion. It is conceivable that subtle and reversible abnormalities underlie "functional" mania and that they are localized in the same cerebral system which is the site of histological lesions in certain organic cases displaying manic symptoms. The time may come when it will be possible to express some constitutional factors in terms of regional susceptibilities of vital centres and mechanisms in the brain and other systems.

A final answer to all these difficult questions will not be given by speculation, however intriguing this may be, but by further experimental and pathological work. In view of the obvious phylogenetic differences, the investigation of human brains containing circumscribed lesions of the relevant centres will be especially valuable. These latter studies should be undertaken irrespective of the mental symptomatology in order to avoid selection of positive cases only. It is with a view to contributing to this collection that my case is presented for publication.

The cerebellum in vitamin deficiency

The cerebellar lesion in our case requires a few remarks. In only one of the five cases on which this paper is based was the cerebellum affected, and the present writer does not recall a description of cerebellar change with a similar selective action on the granules in the literature upon nutritional deficiencies. In chronic alcoholism, with or without the Wernicke syndrome, most writers either failed to find cerebellar lesions (Stevenson, McGowan and Allen, 1941), or described only circumscribed lobular atrophy with degeneration of the Purkinje cells (Neuburger, 1931). In experimental thiamine deficiency, petechial hemorrhages may occur in the cerebellum together with the changes in other regions characteristic of the Wernicke syndrome (cf. Wolbach and Bessey, 1942). Gross hemorrhages in various parts of the brain including the cerebellum have been produced by Jervis (1942) in choline-deficient rats. Alexander (1941), who made an attempt at correlating the various neuropathological lesions with the pathogenic factors operative in chronic alcoholism, is inclined to ascribe an affection of the cerebellum to deficiency of α-tocopherol. It is true that in newly hatched chicks this deficiency may lead to an ischemic necrosis characterized by edema, rapid necrosis of the neurones and of the glia, but it is neither found in adult animals nor in man (Pappenheimer, 1942; Wolf and Pappenheimer, 1942). In none of our cases of histologically verified pellagra was a cerebellar lesion of the type under discussion seen. Only in one doubtful case did the cerebellum display major changes, but their relationship to the pellagra-preventing factor remains to be proved.

A more or less selective degeneration of the granular layer has been described after prolonged experimental CO poisoning (Ferraro and Morrison, 1928), in various toxic-infectious conditions including experimental lead, carbon monoxide, and histamine poisoning, experimental anitoxin, septic meningitis, etc. (Williams, 1934), and quite recently by Winkelman (1943) in one case of diabetes dying from hemorrhagic gastritis and intestinal gangrene, and in another diagnosed as mania. The histological appearance is that of fusing of the granular cells into smaller and larger clumps (conglutination) and subsequent degeneration and disappearance in cases of longer standing.

An interesting light on the pathogenesis of this type of lesion is thrown by recent poisoning experiments with thiophen (Upners, 1939). It has been shown earlier that after massive doses of this substance the Purkinje cells undergo ischemic or homogenizing degeneration. Using small doses over long periods, Upners found a selective action
on the granular layer resulting in degeneration. At the same time he noticed changes in the quadri-geminal region which, in his opinion, closely resembled those seen in the Wernicke syndrome. Unfortunately, his clinical notes were only brief, but he mentioned that the prolonged poisoning resulted in frequent vomiting and complete anorexia in his animals.

There is, thus, some suggestion that a nutritional factor might be operative in the production of selective granular degeneration. A final decision must be deferred, however, until more convincing evidence is available. The problem in its broader aspects is, at present, under investigation in this laboratory.

Changes in the inferior olives

In four out of our five fully examined cases of the Wernicke's syndrome changes were found in the inferior olives. They are illustrated in Figs. 8–12. Fig. 8 shows an approximately normal olive as control. Fig. 9 is taken from the case of gastric carcinoma. It is easily seen with low magnification that there is a diminution of nerve cells which is most conspicuous in the dorso-medial corner of the centre. High-power inspection reveals that all nerve cells show some pigment degeneration, but in the dorso-medial corner they become opaque discs with the nuclei either dark and shrunken or breaking up into granules. This is the cell change known as homogenizing degeneration. There is considerable gliomesodermal reaction ("gliarasion," activated astrocytes, endothelial proliferation) in this corner, and in Holzer preparations a moderate diffuse glial fibrosis is seen. No demyelination was noted. Fig. 10 shows an almost complete loss of nerve cells with low magnification. With higher magnification many nerve cells are still recognizable in advanced condition of homogenizing degeneration. There is also heavy glial and endothelial reaction and severe gliosis in Holzer preparations. The photograph is taken from a case of Wernicke's syndrome in pernicious anaemia. Fig. 11 illustrates a picture, seen in the caudal part of the inferior olives in a case of Wernicke syndrome after hyper-emesis gravidarum. Here again the dorso-medial corner is especially affected. The transition from less affected to the severely damaged part within the dorsal band is shown with higher magnification in Fig. 12. Towards the rostral end of the centre, the whole olive is involved. Histological detail is much the same as in the previous cases, that is to say, the principal features are homogenizing degeneration of nerve cells, and gliomesodermal reaction. The homogenizing cell disease is particularly characteristic. Many naked triangular nuclei with swollen nucleolus are seen as remainders of the affected cells. Again, there is no demyelination. In a last case (pernicious anaemia) the only local sign of olivary involvement is a glial nodule in the medi-dorsal corner, but there is some general gliomesodermal activity throughout the centre.

Lesions of the inferior olives of the type described have been first studied systematically by von Braunmühl (1928, 1929, 1930) in a variety of conditions. Von Braunmühl regarded them as a manifestation of a system disease of the centre, but later, impressed by the type of cell degeneration and gliomesodermal repair, he inclined more to a vascular pathogenesis, and as such they have been accepted by many workers especially of the German school. Subsequently, Neuburger (1931) described identical changes in the olives of alcoholics (his cases 1, 2, 7, 17, 23, 28), in most of which the typical mammillary changes were also seen. Kant (1932/33), Campbell and Biggart (1939) and Alexander (1940) do not mention the olives as vulnerable centres in the Wernicke syndrome. In our own material four out of five fully investigated cases displaying mammillary changes of varying degree had changes in the olives, and it is interesting that none of the cases had an alcoholic history, but had acquired the lesion in the course of pernicious anaemia, hyperemesis gravidarum and severe gastric disease. Scrutinizing von Braunmühl's clinical records one is struck by the frequency with which he found the olivary changes in conditions which are known to facilitate nutritional deficiency (protracted pyaemia, sepsis following abortion, typhoid and paratyphoid fever, postencephalitis after long fever therapy). In only one case (glioma of temporal lobe with intense edema) was there no evidence of a possible nutritional factor. In a fairly large sample of anoxic and vascular conditions, the present writer failed to find olivary changes of this type, nor was this type of olivary degeneration seen in a large series of cases dying in the course of postencephalitis. The only condition in which a comparable change was found was a case of subacute yellow atrophy of the liver.

All this is strongly suggestive of a nutritional factor in the pathogenesis of the olivary lesions. It must be left undecided whether thiamine or some other factor, alone or in combination, is responsible. The histological appearance of the olivary changes is certainly different from that in any other region vulnerable in thiamine deficiency, the main point of difference being the absence of the characteristic primary proliferation of blood vessels. The vascular proliferation must be regarded as secondary to the parenchymatous degeneration. Furthermore, there is no parallelism in the intensity of the lesions. Our alcoholic case with heaviest mammillary damage showed no involvement of the inferior olives, and none of the other vitamins is known to cause olivary lesions if deficient, while in all cases of human pellagra available for investigation at this laboratory the olives were found intact. The identification of the factor responsible for the olivary lesion must be left to specially designed animal experiments.

It is difficult to account for the special susceptibility of the dorso-medial part of the centre. Von Braunmühl has been at a loss to explain it by peculiarities of the blood supply. Olive changes may be secondary to cerebellar degeneration and it is assumed that the olivary axons terminate as
Fig. 8.—Nissl stain, $\times 14$. Normal inferior olive.

Fig. 9.—Nissl stain, $\times 15$. Inferior olive showing degeneration and outfall of nerve cells especially in the dorso-medial corner.

Fig. 10.—Nissl stain, $\times 21$. Inferior olive. Generalized outfall of nerve cells.

Fig. 11.—Nissl stain, $\times 20$. Inferior olive. Degeneration in dorso-medial corner.

Fig. 12.—Nissl stain, $\times 36$. The same as Fig. 11, with higher magnification to demonstrate the contrast between severely damaged (right) and better preserved part of the inferior olive.
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mossy fibres around the dendrites of the granular cells (Parkes, Weber and Greenfield, 1942). According to these authors quoting earlier work, the dorsal part of the olives is related to the cortex of the superior surface of the cerebellum. Likewise, the medial portion of the olives has a close relation to the palaeocerebellar cortex. However, in three of our cases with olivary lesions the cerebellum was histologically normal while in the fourth the cerebellar lesion was ubiquitous. This suggests that the affection of the inferior olives is independent from a histologically recognizable lesion of the cerebellum.

Summary

A pathological investigation has been made in seven cases presenting the Wernicke syndrome. In two cases there was a history of alcoholism and in three of pernicious anaemia, in one the condition followed hyperemesis gravidarum and in one it followed gastric carcinoma.

The last case has been described in full, as it was distinguished by an atypical clinical course in which mania was present for a considerable time. It was important that the oldest and severest lesions were localized in the anterior portion of the hypothalamus. The incidence of manic syndromes associated with hypothalamic lesions has been discussed in the light of previous experimental and pathological observations.

The same case of gastric carcinoma had a peculiar cerebellar lesion affecting predominantly the granular layer.

In four out of the five cases which were fully investigated inferior olives were damaged in a characteristic way, the neurones of the medio-dorsal corner undergoing homogenizing degeneration. The possibility of a deficiency factor in the pathogenesis of the olivary lesions has been discussed.

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