Medicinal Treatment.

Arsenic has long been recognized as the most useful drug, and the upholders of the spirochaetal theory lay emphasis on this fact. Where possible, early cases should receive precisely the same treatment as that used in neurosyphilis; the dose of intravenous novarsenobillon should, however, never exceed 0.6 gram. Failing intravenous injection, intramuscular preparations of arsenic or bismuth should be given. When such methods are for any reasons impracticable, Fowler's solution should be administered by the mouth, and may be used as a variant to the intravenous and intramuscular methods.

Pyrexial Treatment.

Protein therapy has been tried during the past few years in the treatment of this disease, and some encouraging results have been reported. A mild degree of protein shock may be produced by an injection of milk. It is preferable, however, to obtain a definite rise of temperature, and it has been found that the intravenous injection of typhoid vaccine produced this result. It is usual to commence with a small dose—for instance, 25 million—and gradually increase the amount so that by the end of six or eight injections the patient is receiving 200 millions. Within a few hours of the injection a rigor occurs, and the temperature rapidly rises to 102° or more. During this period there is, of course, general malaise and usually a temporary exacerbation of the symptoms, especially diplopia and spasticity. The injections should be given every fifth day or so, and it is best to give a small dose of novarsenobillon on the day following the injection. This form of treatment should be repeated from time to time. Malaria has also been tried; reports from Vienna are not encouraging in this respect, but Dreyfus and Hanau,¹⁴ in a recent paper, express the opinion that it is more satisfactory than typhoid vaccine treatment. Dr. F. Golla informs me that relapsing fever has replaced malaria at the Maudsley Hospital in the treatment of general paralysis of the insane, and that the results are just as satisfactory as with malaria, and the risk of a fatal termination is considerably less. Relapsing fever might therefore prove more suitable than either malaria or typhoid vaccine as a pyrexial agent in disseminated sclerosis.

It is not easy to say whether any of these various forms of pyrexial treatment are of any real value; the natural mutability of the disease and the comparatively short time that this form of treatment has been on trial have both to be remembered. In a well established case which is more or less stationary I feel sure that no such treatment is of the least use. On the other hand, in a moderately severe case of relatively short duration, in which the disease is obviously active, pyrexial treatment does sometimes appear to bring about a remission. In early cases the chances of arresting the disease, even though temporarily, are greater, and remissions occurring within a short time of the treatment are not uncommon. It may be argued that such remissions are independent of the treatment, and would have taken place in any case. That may be so, but at least such remissions, whatever their cause, do not contraindicate this line of treatment.

In conclusion, it is evident that little advance has been made in the treatment of disseminated sclerosis, and no real progress in this direction can be looked for until we know more of its etiology. The exogenous theory of this disease, though it may seem at first glance to be wild and speculative, is one that may repay further study.

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THE PATHOGENESIS OF RESPIRATORY ANOMALIES AFTER EPIDEMIC ENCEPHALITIS.

BY

MACDONALD CRITCHLEY, M.D. BRISTOL,

M.R.C.P. LOND.,

LATE RESIDENT MEDICAL OFFICER, NATIONAL HOSPITAL, QUEEN SQUARE,
LONDON.

AMONG the many mental and physical after-effects of epidemic encephalitis the respiratory disorders are now recognized as occupying a very definite place. Knowledge of this aspect of the disease has gradually accrued by the publication of numerous isolated case reports.

GROUPING OF CASES.

In an earlier paper¹ we pointed out that encephalitic respiratory disorders may occur both in the acute stage and also as "sequelae." The symptoms on analysis may be resolved into three main groups: (1) disorders of the respiratory rate, (2) disorders of the respiratory rhythm, and (3) respiratory "tics." Combinations of these groups often occur, and any of these manifestations may be constant, though more usually they are intermittent.

Respiratory Rate.

The disorders of the respiratory rate comprise acceleration (tachypnoea) and depression (bradypnoea). There is usually no alteration in the pulse rate, no cyanosis, and no thoracic distress in these varieties. In some instances the disorder supervenes only when the patient is supine, in others only when the patient stands upright. In other cases, again, the acceleration in respiration rate only comes on during sleep. The onset is frequently determined by emotional disturbances, such as those occasioned by fright, shyness, or excitement; the attack can often be checked temporarily by a strong effort of will on the patient's part. Again, the attack can frequently be cut short by speaking sharply to the patient or by ordering him to hold his breath, breathe through his nose, or perform some complicated act which will necessitate the patient's close attention. Consciousness is usually retained throughout an attack, but on rare occasions may be lost.

In some instances the lungs become over-oxygenated during the tachypnoeic spells; carbonic acid is washed out of the circulation and the acid-base balance is altered in the direction of a temporary alkalosis. Such a metabolic change results in tetany, of which some half-dozen cases following post-encephalitic tachypnoea are on record.

Bradypnoea is a much rarer manifestation, but may be met with during both the acute and chronic stages. The respiratory rate may fall as low as 6 per minute, and, in order to maintain full oxygenation of the blood, each breath is usually of greater amplitude than normal.

Respiratory Rhythm.

Disorders of the respiratory rhythm comprise those in which there is an irregular spacing in the normal cycle of inspiration: expiration. Such an arrhythmia may be regular or irregular in its metre; it may be paroxysmal or continuous in appearance. The arrhythmia may be apparent during the waking state only, or, conversely, only when sleeping. In other instances it may occur whether the patient is awake or asleep.

Sighing.—This is perhaps the commonest example of a respiratory dysrhythmia, and is often so slight in degree as to escape casual observation. It is especially common in association with Parkinsonism. From time to time the patient takes a deep inspiration followed by a prolonged expiration. A short period of compensatory apnoea usually follows. These sighs occur without any apparent reason at intervals throughout the day or night, often without the patient's knowledge.

Apnoeic Pauses.—Occasionally a patient can be observed to hold his breath in the middle of normal respiration without any preparatory acceleration of rate or depth and without any previous sighing. More commonly the apnoeic pause is ushered in by a series of deep gasping respirations,

which may be either slow or rapid in rate. The breath is then held as though voluntarily, in the phase of full inspiration, until the face and neck become suffused and deeply cyanosed. In cases of prolonged inspiratory apnoea consciousness may be temporarily obfuscated and convulsive attacks are not uncommon. In the less severe degrees of this condition the patient performs many grotesque gestures, clenching and unclenching his fists, clawing the air, or twitching. At the end of the apnoeic spells the breath is audibly expelled, and then there follows a shorter period of expiratory apnoea before the resumption of normal breathing.

The drawing reproduced herewith shows a patient suffering from a post-encephalitic respiratory disorder in an actual attack. The patient, a young man aged 25, had been attacked with acute

epidemic encephalitis in December, 1924. The respiratory disorder started originally as a persistent dry cough; later the patient developed attacks of breath-holding, occurring many times daily. In the attacks the patient stands up and takes several deep noisy breaths in rapid succession; next he stiffens himself and slowly bends the trunk backwards, at the same time extending the head fully. The arms are raised from the sides to a right angle in an exaggerated "yawning attitude." The forearms are alternately flexed and extended, the hands being maintained in the "accoucheur's attitude" characteristic of tetany. During this time the breath is held in full inspiration; the abdominal muscles are tightly contracted and the veins of the face and neck become extremely engorged. Each spasm is maintained for twenty to thirty seconds; in some instances there is a transient loss of consciousness and the patient falls. The attacks are

terminated by a long expiration followed by a short spell of noisy tachypnoea. No physical signs suggesting any degree of Parkinsonism could be discovered. Drawing (from photograph) by Miss D. Pillers, Bristol.

"Cogwheel" Respiration.—A common type of anomaly seen after encephalitis consists in respirations which are jerky and broken in character. The jerkiness is usually more obvious during the expiratory phase. When viewed on a fluoroscopic screen it will be observed that the diaphragm is rising and falling in a series of cogwheel-like movements, and it is probable that this defective diaphragmatic movement is responsible for the peculiar respiration. In cases of the myoclonic variety of encephalitis the diaphragm and other respiratory muscles may participate in the myoclonus, producing a correspondingly jerky character to the respiratory rhythm.

Bigeminal and Trigeminal Respiration.—Analogous to the well known pulsus bigeminus or trigeminus, the respiration rate may take on a regularly alternating character. Thus the breaths may be alternately deep and shallow, or one deep respiration may be followed by two of shallower degree.

Respiratory "Tics."

The varieties of respiratory mannerisms met with in children after epidemic encephalitis are manifold; many of them are usually regarded as instances of "habit spasm." These diverse types may be aggregated and considered under the title of "respiratory tics." They are commonest in children, and may in fact be the only outstanding symptom remaining after encephalitis. More commonly they are associated with psychical and sleep abnormalities,

in the absence of gross organic change. Amongst such "tics" one includes the spells of spasmodic cough occurring without any adequate laryngeal, tracheal, or pulmonary abnormality. Another example is found in the "blowing" habits of some post-encephalitics. The patient, usually a child, will suddenly leave off what he was doing, and, inflating the cheeks, give vent to a series of rapid blowing expirations. The child cannot give any adequate reason for his peculiar behaviour. Sniffing constitutes another objectionable post-encephalitic "tic." Expiration of air through the nose—spoken of as *soufflement* by the French—is another similar habit.

Wide gaping of the mouth, occurring from time to time without adequate reason, is commonly observed after encephalitis, especially in association with Parkinsonism. Sometimes the mouth is opened so far as to bring about an actual subluxation of the jaw joints. The patients, on inquiry, state that they have no sensation of fatigue, but that the lower jaw seems to drop of its own accord. They are unable to check the yawning for longer than a few minutes.

GENERAL CONSIDERATIONS.

Many attempts have been made to explain these phenomena; whilst certain observers have been content to dismiss these disorders as hysterical manifestations, the majority of physicians regard them as resulting from definite organic lesions in the central nervous system.

Supporters of the former conception stress the diversity of the clinical manifestations, their inconstancy, and the theatrical and bizarre nature of the accompanying gestures. They emphasize the emotional instability of many of the patients, and their susceptibility to environmental factors. The precipitation of the attack under psychical stress, its aggravation by excitement, and lastly its frequently abrupt arrest by strong suggestion, are also quoted. The similarity of the respiratory "tics" to the well recognized habit spasms of childhood is another argument. They point out, too, that similar respiratory anomalies—tachypnoea, periodic apnoea, Cheyne-Stokes breathing, sniffing, coughing, and other tics—have all been described long ago by Janet and others as well recognized manifestations of hysteria. Recently there have appeared publications endeavouring to trace a psychical origin to the nervous and respiratory sequelae of encephalitis.

It must be conceded, however, that none of these arguments are conclusive. Many of the late manifestations of encephalitis—such, for example, as tremor—are similarly influenced by the emotional state of the patient. Thus, apprehension, fear, pleasure, are all factors which aggravate the tremor, though few would affirm that this was a symptom of psychical origin; most patients exhibiting the Parkinsonian syndrome are able to control the tremor for a short time by exercising a strong effort of will, just as many of the patients with tachypnoea can alter temporarily their respiratory rate, and make themselves breathe slower or deeper, shallower or faster. Far from being an indication of hysteria, therefore, this variability of symptoms depending upon different states of emotion and control is known to occur in many organic disorders. In all genuinely hysterical cases of disordered respiration other characteristic features of hysteria can readily be demonstrated. The course of the disease, moreover, is very different in the two conditions: in hysteria the respiratory anomaly is usually transient and rapidly yields to treatment by suggestion; in the post-encephalitic states, however, the outlook is grave—a few improve, some remain stationary for months, but the majority tend to become progressively worse, the physical and mental states simultaneously deteriorating. Many eventually drift into asylums, being affected with delusions and hallucinations, often highly systematized. It does not seem necessary, therefore, to seek for a psychical origin to the respiratory disorders of encephalitis any more than in any other organic psychosis; diffuse histo-pathological changes are readily demonstrable, and although the anatomical basis of such manifestations is still a matter of hypothesis, the physiology clearly entails a dissolution of the highest functions of the mind—judgement and inhibition.

Normal Physiology of the Respiratory Mechanism.

Normal automatic or unconscious breathing is effected through a so-called "respiratory centre," which is in reality made up of a number of anatomically separate areas situated in the pons and medulla. This centre is stimulated partly by afferent proprioceptive impulses from the alveoli of the lungs and the thoracic musculature, but mainly by the concentration of carbonic acid in the blood stream. The efferent impulses are conveyed along the lower neurones to the chest muscles and diaphragm.

Though the respiratory centre normally acts independently as a reflex phenomenon, it can be influenced by cortico-bulbar activity. Thus voluntary impulses, conveyed along the pyramidal tract, are capable of inhibiting or accelerating the respiratory centre so that an individual is able, temporarily at least, to hasten or retard his respiration rate, to take shallow or deep respirations, to assume an irregular rhythm, or to inhibit all respiration. Moreover, the respiratory centre is under the influence of other cortico-spinal impulses, which are correlated with the various respiratory irregularities occurring under emotional stress. Thus fright is associated with a temporary inhibition of respiration; pleasurable excitement with an acceleration. The gasping respirations which accompany crying and sobbing also illustrate the influence of the emotions upon the activities of the respiratory centre. There is a good deal of evidence—both experimental and anatomical—to suggest that these phenomena are conveyed along very definite psychomotor pathways. Spencer has demonstrated that these tracts originate in the prefrontal cortex and pass in close proximity to the optic thalamus to end in the lower pons. It is along these routes that the characteristic facial movements and respiratory changes are affected with emotional stimuli. It appears also that the pyramidal tract exercises partial inhibition over these psychomotor (or facio-respiratory) pathways; hence marked emotional instability and even spasmodic laughter and weeping after bilateral ablation of the pyramidal tracts are observed, as in pseudo-bulbar palsy. This normal inhibitory effect of the pyramids, though taking place partly in consciousness, is mainly a subconscious influence, and probably depends anatomically upon the presence of transcortical projection fibres between the precentral and prefrontal cortices.

The Disorders of Respiration.

The pyramidal tract cannot be implicated in the clinical manifestations of disordered respiration because of the absence of the characteristic changes in reflexes and the conservation of voluntary control. The respiratory centre itself does not appear to be the site of disease; there is little or no similarity in the diverse respiratory disorders to the dyspnoea of bulbar disease. It is improbable, too, that a medullary lesion would affect the centres subserving respiration and spare the other important nuclei closely aggregated in this region. Moreover, pathological evidence has failed to support this theory. Changes in the proprioceptive impulses or alterations in the chemistry of the circulating blood have never been demonstrated; the afferent stream of impulses to the medulla therefore seems to be intact. The efferent neuro-muscular mechanisms have been held responsible by some; it is improbable, however, that any such changes are present in all the types of disorder, although doubtless they are a factor in some. Thus rigidity, myoclonus, or tremor of the diaphragm can be demonstrated in patients showing a cogwheel type of respiration. It is obvious, however, that the pathogenesis of respiratory disorders as a whole is to be sought outside the efferent pathways.

Psychical and Sleep Disorders.

Stress has been laid upon the frequent occurrence of psychical and sleep disorders in association with respiratory upset; the association with the emotional instability of the patient lends weight to the view that the psychomotor pathways, with their transcortical projections, are the probable site of origin. An interruption in these latter fibres would abolish the unconscious control normally exercised by the pyramids over the emotional factors of respira-

tion; we would expect, then, to encounter an unstable type of respiration, influenced by every variety of emotional play. The conscious and voluntary control, which we believe to be the function of the long cortico-bulbar fibres of the pyramids, persists; consequently the patient is able, by exerting a determined effort of will, to check or even arrest the abnormality of breathing. Many of these respiratory upsets are of a striking and alarming nature even to the onlookers. It is not surprising that the patient himself is profoundly impressed by the phenomena, and the emotion of fear thus engendered tends to maintain the abnormal respiration. The disease tends, therefore, to perpetuate itself, owing to the complete emotional instability and the lack of equanimity and self-confidence.

Reference has been made to the occurrence of respiratory disorder during sleep; many authors have pointed out that towards nightfall the patients become restless and excited, and frequently noisy and unruly—in striking contrast to their diurnal somnolence and placidity. Simultaneously there is an aggravation in the respiratory disorders. These facts can be reconciled with a tiring-out of the processes of inhibition which have been active throughout the daytime, so permitting conduct and respiratory anomalies to manifest themselves unchecked.

The researches of Pavlov have done much to throw light upon the physiology of the highest cortical processes; they have revealed that many of the seemingly complex activities of the cortex are in reality the resultant of definite conditioned reflexes and their antagonistic inhibitory influences. The study of behaviour in animals after ablation of small areas of cortex demonstrates that there is a temporary upheaval of the normal conditioned reflexes, and that the inhibitory processes are affected to a much greater extent than the excitatory. More extensive damage to the brain produces a permanent weakness of the inhibitory processes. A similar state of affairs appears to exist in many cases of post-encephalitic respiratory disorder, where there is an obvious impairment of inhibition on the part of the patient, although the conditioned reflexes can still be checked temporarily by unexpected extraneous stimuli (external inhibition).

It appears, therefore, more in accord with the modern conceptions of neurology to regard these "psychical" changes following encephalitis (conduct and sleep disorders, respiratory abnormalities) as essentially physical in origin. I submit that the respiratory disorders are essentially organic in their pathogeny, and suggest that they arise from disorder of the psychomotor pathways controlling the respiratory centres, together with a defective inhibition by cortical control.

REFERENCE.

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EXPERIMENTS ON THE RADIATION OF
TUMOURS.

WITH SPECIAL REFERENCE TO THEIR BLOOD SUPPLY.

BY

J. C. MOTTRAM, M.B.LOND., D.P.H.CANTAB.

(From the Research Laboratory, Radium Institute, London.)

THE clinical treatment of tumours by radiation brings out two outstanding facts: first, that there are wide differences in the sensibility of tumours of different kinds; and secondly, that tumours of the same kind in different patients also vary in sensibility, though the variations are less wide than when tumours of different kinds are compared. At present there is no way of estimating these differences before treatment. The first kind of variation has been considered to reside in the tumour cells, but when different kinds of tumour cells are irradiated *in vitro* the lethal dose is found to vary very little. The second kind of variation must reside in the patient, and has been assumed to be due to a resistance towards tumour growth, which varies from patient to patient. Thus, it is evident that we have no certain explanations for the two most important clinical facts, and in order to elucidate them the following experiments have been carried out.

When a tumour is radiated *in vivo*, then removed at once,