IT IS a curious fact that while most physicians have a strong bias toward an organic etiology of mental disturbances, at the same time they seem to have little interest in and, indeed, often completely overlook delirium, the one mental disorder presently known to be based on derangement of cerebral metabolism. This state of affairs persists in spite of the fact that many seriously ill hospitalized patients experience some degree of delirium during the course of their illness. The explanation for this state of affairs is not difficult to find. In the first place, the deficiencies in the education of many physicians ill equip them to recognize any but the most flagrant examples of delirium, much less to differentiate it from other types of psychologic disturbance ordinarily encountered among medically ill patients. Most delirious patients are considered either dull, stupid, ignorant, or uncooperative. It is only when their behavior and content of thought are grossly deviant that an abnormal mental state is recognized, although it is not always correctly identified as delirium. Only the latter type of patient, often a management problem on a medical or surgical service, is likely to result in a psychiatric consultation. The psychiatrist, on the other hand, is likely to see only the more disturbed delirious patients since he is generally called in consultation only when someone is disturbed by the patient’s behavior. Hence, not only may his picture of delirium be a restricted one, but also, seeing the patient in the home territory of the “organic” specialists, he is less likely or able to pursue an understanding of the underlying physiologic derangements, which are generally conceived to be the proper domain of the internist. Unhappily, the unfortunate patient’s malfunctioning brain rests in limbo, an object of attention and interest neither to the medical man nor to the psychiatrist.

This unsatisfactory state of affairs is not helped at all by how the matter is handled in either the medical or the psychiatric texts. The student who hopes to find some clarification of these matters in modern textbooks will gain only confusion. The more modern textbooks of psychiatry follow the official system of classification adopted by the American Psychiatric Association, whereby delirium is correctly included among the disorders caused by or associated with impairment of brain tissue function.\textsuperscript{1,2} But these are then subdivided into acute

\textsuperscript{1,2}This work was supported in part by a grant from the Foundations Fund for Research in Psychiatry.
and chronic brain disorders, which are classified in etiologic terms, such as disorders due to or associated with infection, intoxication, trauma, circulatory disturbance, etc., as if each represented a clinical entity. The unwary student is plunged directly into a consideration of such supposed specific entities with either no or only a very sketchy consideration of the basic processes underlying and characterizing delirium. There is little or no indication of the frequency of this syndrome or consideration of the various ways in which brain function may become disordered in relationship to the physiologic derangements characterizing organic illness. By inference the reader is led all too easily to associate delirium with certain specific entities, e.g., meningooccal meningitis, chorea, encephalitis, bromides, alcohol, head trauma, myxedema, and so on, and to overlook the fact that in most instances multiple factors are operating, sometimes only indirectly related to the primary diagnosis.

The textbooks of medicine are even more cavalier in their treatment of this subject. In some it is mentioned only in passing as a complication of certain illnesses, as in yellow fever or typhoid. Perhaps the best discussion is found in Harrison's work, but this is somewhat misleading because of the author's bias for the alcoholic patient as depicting most perfectly the picture of delirium. Further, it is surprisingly lacking in any consideration of the physiologic and metabolic factors.

The problem of delirium is far from an academic one. Not only does the presence of delirium often complicate and render more difficult the treatment of a serious illness, but also it carries the serious possibility of permanent irreversible brain damage. With increasing life expectancy and with improved survival through the influence of surgery and antibiotics, we are now beginning to see an increasing incidence of so-called senile and arteriosclerotic dementias. Do we know how often such developments are initiated during delirious episodes experienced in the course of serious illness? Bedford has recently shown that dementia not infrequently develops in old people following operations under general anesthesia and after shock in the course of serious illness. The physician who is greatly concerned to protect the functional integrity of the heart, liver, and kidneys of his patient has not yet learned to have similar regard for the functional integrity of the brain. This is a serious and, perhaps, tragic omission. It is our hope that this paper will stimulate among physicians in general, and among clinical investigators in particular, more frequent recognition of and greater interest in the syndrome of delirium.

DEFINITION

Before attempting to define delirium in clinical terms, we wish to establish firmly what we believe to constitute the basis for this syndrome. In the title the term "syndrome of cerebral insufficiency" is used. This draws attention to the basic etiology of all delirium and couches it in terms analogous to the more familiar concepts of renal insufficiency, hepatic insufficiency, cardiac insufficiency, etc. As with the more familiar types of organ insufficiency, this refers to what evolves when the function of the organ as a whole is interfered with, for whatever
reason. Whether applied to the liver, kidney, or brain, this can be reduced to two basic underlying processes, namely, the failure of metabolic processes to maintain the function of the organ or the loss through death of enough functioning units (cells) to render the function of the organ insufficient. It will be recognized that the first situation may evolve into the second and that except in situations of rapid and massive process, both must often co-exist. Further, the first situation may have a high potentiality of reversibility, a possibility not likely when there is cell death unless the organ has the capacity for regeneration of its functional units, which the brain does not. With respect to the brain, this also corresponds to the clinical distinction between delirium and dementia. Delirium refers to the more reversible disorder and dementia to the irreversible disorder. While such a distinction has some pragmatic value, it would be a mistake at this time in our knowledge to regard these states as any more than different degrees or stages of similar processes. This is especially so since clinically many patients manifest a lower threshold to delirium in response to some general physiologic derangement by virtue of having already suffered some loss of brain substance (i.e., dementia), although the latter may have been so well compensated as to have been clinically inapparent. Sometimes the concept of acuteness is associated with delirium and chronicity with dementia—but this is not correct. Some types of delirium, such as those associated with pernicious anemia and myxedema, may develop very slowly and last for weeks or months and yet be largely reversible when appropriate therapy is administered. Similarly, an irreversible defect, a dementia, may develop abruptly, as after a severe head injury, prolonged anoxia, or carbon monoxide intoxication. If the cerebral insufficiency develops very abruptly, in a matter of a few seconds, and lasts only seconds, the resulting disorder is syncope, but again we should appreciate that the basic process is essentially the same as that in delirium. Indeed, we know that if the unconsciousness of syncope persists beyond 30 to 60 seconds, the victim usually will pass through a period of delirium before complete recovery is achieved, whereas with the longer lasting faints, permanent damage and dementia may result. In other words, clinical convention leads us to delineate a number of syndromes associated with cerebral insufficiency, and it is well for the physician to appreciate the common denominator shared by delirium and these other syndromes. In all instances, the factors maintaining the metabolism, the functional integrity, and the life of the cell are of primary importance.

THE METABOLISM OF MAMMALIAN BRAIN

Further progress in the understanding of the etiology, treatment, and prevention of delirium is linked irrevocably with our advancing knowledge of cerebral metabolism. For a long time progress in this field has been slow and uncertain, and few have seriously interested themselves in it. The last decade has, however, seen a great surge of interest and progress, as indicated by the founding of the Journal of Neurochemistry in 1956 and the holding of two International Neurochemical Symposia. We will make no attempt even to summarize the important recent advances but would refer the interested reader to the two volumes con-
It is misleading to speak of brain metabolism in any unitary fashion since it is becoming clear that not only may there be major differences in the metabolism of the neuron or nerve pathways compared to the supporting structures, but also that there are significant differences in the metabolic activity of the various regions of the brain. Lowry has developed an elegant technique which makes feasible the measurement of enzyme concentrations in single cell bodies and related structures and has demonstrated significant differences in the activities of 9 enzymes in cell bodies and related structures taken from 6 different areas of the brain.

There is need for caution in accepting too easily the classic generalization that "brain" derives its energy entirely from aerobic processes and that glucose is the only substrate. While clinical observation and in vivo studies leave no question that both oxygen and glucose are essential to maintain higher nervous (and mental) activity, the exclusive emphasis on this fact has tended to obscure other biochemical derangements that may take place in spite of adequate oxygen and glucose supplies. Even this dependence on aerobic processes to maintain the normal state of the brain may vary. Shapot, for example, has shown that the susceptibility of the brain to hypoxia varies with the level of functional activity of the central nervous system. He claims that resistance to hypoxia is increased by inhibition and falls after severe excitation. If verified, this phenomenon is one which could have very great clinical importance in respect to the susceptibility to develop delirium. It is a common clinical observation that an organic syndrome (usually dementia) may develop rapidly after a period of psychologic stress. Shapot has also pointed out that the energy produced by the cell is utilized in two ways, namely, for "structural metabolism" (renewal of cell structures) and for specialized functional metabolism. Obviously such a distinction between structure and function is only a relative one, involving as it does relative rates of chemical reaction underlying various processes. Nonetheless this does introduce the possibility of competition between these two kinds of metabolism, as when there is an excessive need or an insufficient supply involving one or another system. In another study, Shapot demonstrated that, when rats were teased to exhaustion, methionine incorporation into brain proteins was much lower than in control animals, whereas, if the exhausted rats were left alone to sleep for 30 minutes, the rate of methionine incorporation was greatly increased as compared with the controls. He interprets these findings to mean that, since during the first minutes of sleep following intense excitation the cerebral respiration still proceeds at a high level and the energy requirements for functional activity are presumably minimal, this energy must therefore be for the requirements of the structural metabolism, which then restores the functional capacity of the nerve cells. Thereafter respiration again falls as the animal continues to sleep.

Other studies indicate that the amino acid and protein metabolism of brain is much more active than heretofore had been supposed. Strecker brings support for the idea that the glutamic acid-glutamine system can act as a homeo-
static maintenance mechanism controlling carbohydrate metabolism and the many metabolic systems which are interdependent with carbohydrate metabolism. Sporn, Dingman and Defalco have recently demonstrated a rapid rate of uptake of intracisternally injected proline by brain protein and the conversion by brain of this proline to glutamic acid, aspartic acid, alanine, gamma-amino-butyric acid, ornithine, and arginine.

The alleged toxic effects of ammonia on the function of the central nervous system, with its suggested relationship to the delirium of liver disease, focuses attention on the processes of ammonia formation in the brain and the mechanisms of its removal, for which the glutamic acid-glutamine system is regarded as the most likely candidate. Weil-Malherbe observed that brain cortex slices form ammonia at a fairly steady rate in a glucose-free medium. This finding is of particular interest in the light of Geiger’s observation that, if cerebral blood flow is increased two- or threefold over normal during a glucose-free perfusion lasting an hour or longer, the electrical activity (EEG) is maintained, reflexes can be elicited, and oxygen consumption of the brain is only slightly below that obtained with glucose. Geiger and his co-workers showed that during glucose-free perfusion structural components are used up by the brain while the preparation still maintains its physiologic functions. These experiments indicate that, given a fast enough cerebral blood flow, the brain can survive and maintain its excitability in the absence of glucose for over an hour by using some of its structural components. Geiger believes this can be explained on the assumption that the breakdown products resulting from noncarbohydrate metabolism in the brain are toxic, but that by speeding up blood flow these breakdown products of noncarbohydrate metabolism are quickly eliminated. This worker also showed that the brain ceases to oxidize glucose, accumulates a high concentration of lactic acid, and loses its physiologic activity in perfusion experiments after about 60 minutes of perfusion without the liver. The insertion of an isolated liver into the perfusion or the addition of fresh liver extract restores cerebral glucose oxidation. A depletion of the galactolipid and phospholipid content of the brain is observed during perfusion in the absence of the liver, but the addition of cytidin and uridin maintains glucose oxidation even in the absence of the liver and prevents the depletion of liquids.

These are but a few of the recent discoveries which invite the clinical investigator to turn his attention to the exploration of similar phenomena in the brain of the patient with delirium.

THE METABOLISM OF THE HUMAN BRAIN

The problem of investigating the metabolism of the intact human brain presents major difficulties. This subject is well reviewed in a recent paper by Kety whose nitrous oxide technique has been the most extensively used method of studying the general metabolism of the brain in vivo. While it has yielded useful results, particularly in respect to the quantity and dynamics of cerebral blood flow, on the whole it has been of limited value in advancing our knowledge of cerebral metabolism in delirium. Some of the reasons for these limitations have been pointed out by Kety. For one thing, since it measures only the total
oxygen uptake of the total brain, it gives no information as to how or even where such energy is being utilized, a point already emphasized when we drew attention to the contrast between so-called structural metabolism and functional metabolism. Thus, it is not surprising that coma is the only situation in which marked depression in oxygen uptake is consistently found. With the lesser degrees of derangement characteristic of delirium, results have been inconsistent. This, we suspect, is more a reflection of a poor design of these studies than a deficiency of the blood flow method itself. The technique usually has been to select for cerebral metabolism studies patients with established diagnosis, such as congestive heart failure, pernicious anemia, hypothyroidism, hypertension, etc., but then to make only a crude evaluation of mental status, often with little understanding of what psychologic and behavioral characteristics could be expected to correlate with reduced cerebral metabolism. In some case reports it seems improbable that the patient was delirious and in others it is impossible to tell from the published material. Further, only a few investigators have made serial observations on the same patients, either during spontaneous recovery or during the application of specific measures which might be expected in any particular instance to improve cerebral metabolism. And in some of the instances in which this was done, the techniques used to evaluate the change in mental status were so inadequate as to limit greatly the significance of the results. In spite of these deficiencies, there is a quite suggestive correlation between the degree of decrease in cerebral oxygen consumption and the mental state in hypoglycemia, diabetes, pernicious anemia, and hypothyroidism. It is our opinion that when more attention is paid to identifying and evaluating those aspects of mental function which are characteristic of delirium and when each patient is used as his own control, a much more consistent correlation between cerebral oxygen uptake and mental status will be established in delirium. Perhaps the main exceptions might be those situations in which increased oxygen uptake is not maintaining the function of the brain but some other processes, such as acute inflammatory reactions in encephalitis.

THE ELECTROENCEPHALOGRAM AS AN INDEX OF CEREBRAL INSUFFICIENCY

At present the electroencephalogram, as an index of functional metabolism, is by far the most sensitive and reliable indicator of cerebral insufficiency, as we have defined it. Indeed, in this respect, the electroencephalogram reflects cerebral insufficiency as reliably, if not more reliably, than the electrocardiogram reflects myocardial insufficiency. In spite of the considerable evidence that has accumulated over the past 15 years, this fact remains little known and even less used, either by investigators or by clinicians. Victor and Adams* state, "The value of the electroencephalogram in studying delirium has largely been limited by the difficulty of obtaining records free of movement artifact. There is some evidence that the EEG in severe delirium shows non-focal slow activity in the range of 5-7 per second, a state which rapidly returns to normal as the delirium clears. In milder degrees of delirium there is usually no abnormality of the EEG." As we shall show, this statement is grossly inaccurate.
Actually, Gerard demonstrated more than 20 years ago that EEG frequency could be expected to parallel changes in the metabolism of the cell, increasing with rise in metabolism and decreasing with fall in metabolism. Polarographic studies demonstrate a very close relationship in time between local reduction of oxygen availability as measured by the electropolarograph and change in the EEG; the latter usually occurs 6 to 8 seconds after the local oxygen tension begins to fall. Both experimental and clinical observations bear this out. For many years it has been known that both hypoxia and hypoglycemia produce slowing of the EEG. These are two physiologic conditions under which it is well established that the metabolism of the brain cannot be successfully supported. With the application of a quantitative method of frequency analysis of EEG, it has been possible to demonstrate significant slowing of the EEG at ambient air pressures equivalent to 12,000 feet and at blood sugar levels below 60 mg. per 100 c.c., changes which increase progressively as oxygen saturation and blood sugar levels, respectively, are further reduced. Indeed, changes in EEG frequency can be demonstrated before any change in psychologic performance becomes demonstrable and well before any change in total cerebral oxygen uptake can be measured by the Schmidt-Kety method. Similar results have been obtained using alcohol, carbon monoxide, and Freon (F12). In all these experimental studies, the fundamental fact has been demonstrated that the psychologic changes correlating most precisely with the slowing of EEG frequency were those that had to do with awareness, attention, memory, and comprehension—that is, the cognitive functions. Observing on different occasions the effects of hypoxia, hypoglycemia, and alcohol on the same subjects, we have demonstrated that, for comparable degrees of slowing of the EEG, the degree of disturbance in cognition, as assayed by clinical tests, was essentially the same under each of these three circumstances. On the other hand, the individual subjects differed appreciably as to their behavior, content of thought, and expression of affect, depending on whether they were under the influence of hypoxia, hypoglycemia, or alcohol. The next section will take up the more detailed delineation of these psychologic characteristics of delirium.

Such studies indicate an approach to the experimental production and study of delirium. We have demonstrated that drugs or physiologic processes that lead to slowing of the EEG also lead to a reduction in the level of consciousness and the efficiency of cognitive processes. We have not observed any circumstance in which under experimental conditions diffuse slowing of the EEG failed to be correlated with such an alternation in cognition or vice versa. For example, the prolonged administration of ACTH or cortisone is occasionally associated with psychotic reactions. ACTH and cortisone produce no change in the EEG frequency of normal subjects and most psychotic reactions occurring during the administration of either ACTH or cortisone are unaccompanied by EEG slowing or by changes in cognitive functions characteristic of delirium. In those few instances in which diffuse slowing does occur, a reduction in the level of awareness has been a consistent feature. Atabrine (quinacrine) administered to normal subjects produced heightened attention and vigilance and increased the frequency of the EEG, resulting in a syndrome which was clinically different from delirium.
Utilizing this experimental technique, it has also been shown that the significant EEG finding is the degree of slowing rather than the absolute frequency.\textsuperscript{27,28,31-3} Thus, if the EEG initially is fast or in the upper range of normal, a significant reduction in the level of consciousness and EEG frequency may be provoked by drugs, alcohol, hypoxia, etc. without the EEG frequency necessarily falling below the accepted normal range.\textsuperscript{37,38,38} It is therefore possible to have a normal EEG in the presence of an appreciable degree of cerebral insufficiency and reduction in the level of awareness, as when a person whose premorbid alpha frequency is 11 to 12 per second shows a slowing to 8 to 9 per second during a moderate delirium. Both of the values still fall within the accepted normal range for the adult population.

The experimental data receive ample confirmation when one examines patients exhibiting varying degrees of disturbance in the level of consciousness and cognitive functioning (as established by the techniques of examination to be described) in the course of any somatic illness. When one studies patients who improve spontaneously or as the result of appropriate therapy, all patients show an increase in the frequency of EEG corresponding to the degree of recovery of the underlying clinical condition and the degree of improvement in the level of awareness.\textsuperscript{34-37} As in the experimentally provoked deliria, a few clinically delirious patients exhibit EEG frequencies within the accepted range of normal, but these also show an increase in frequency on improvement, indicating that their premorbid EEG had been in the fast range. When physiologic derangements can be corrected, as with the administration of oxygen to the patient in congestive failure, the change from the recumbent to the sitting position in the patient with pulmonary edema, the administration of glucose to the patient with spontaneous hypoglycemia, or the transfusion of blood to a patient with very severe anemia, then changes in EEG frequency and in mental state may take place rapidly and always to a corresponding degree.\textsuperscript{37} The majority of patients with untreated pernicious anemia have slow EEG's and reduced levels of awareness and both of these abnormalities respond rapidly to the administration of Vitamin $B_{12}$ or liver extract.\textsuperscript{34} Of interest is the fact that in pernicious anemia the improvement in EEG and in mental status corresponds in time with the beginning of the reticulocyte response and antedates by a considerable period the rise in hemoglobin. This we consider as evidence that the pernicious anemia process includes a cerebral metabolic defect independent of the oxygen-carrying capacity of the blood, a finding which may be related to Geiger's findings noted previously.\textsuperscript{18} Addison's disease and hypothyroidism are two other conditions in which such EEG abnormalities occur with great regularity and respond specifically to appropriate hormone therapy.\textsuperscript{35,37}

All these clinical and experimental studies have revealed that the degree of slowing of the EEG corresponds best with the disturbance in consciousness; that these EEG changes are reversible to the extent to which the underlying pathophysiologic process is reversible; and that the character of the EEG change is independent of the specific underlying disease processes but is more related to its severity and duration. On the other hand, there is little correlation between
the degree of EEG change and the more personal aspects of behavior, as will be described.

THE CLINICAL SYNDROME: DELIRIUM

We thus arrive at the proposition that a derangement in functional metabolism underlies all instances of delirium and that this is reflected at the clinical level by the characteristic disturbance in cognitive functions and at the physiologic level by the characteristic slowing of the EEG. To express this slightly differently, a reduction in the level of cognition is a sine qua non of delirium; a relative generalized slowing of the EEG is a sine qua non of delirium, the clinical expression of a cerebral metabolic defect; the diagnosis of delirium is unequivocally established when it can be shown that the level of awareness correlates with changes in EEG frequency, reduction being accompanied by further slowing of the EEG and improvement by relative acceleration of the EEG.

Before describing in more detail the identifying psychologic characteristics of delirium, it might be well to comment on the inadequate and confusing fashion in which delirium and the behavior of delirious patients are referred to in the literature. While there are virtually no papers on delirium per se, hospital records and the medical literature abound with case reports involving patients who are delirious by the criteria we have established. In some papers the evaluation of the mental state is an important correlate of other physiologic or pathologic processes that are the subject of investigation. Yet it is common to find such statements as: "The patient was disoriented but not delirious." "The patient was confused and agitated, almost delirious." "He was confused and lethargic and became delirious at night." "He was intermittently obtunded and hallucinating." "The patient became uncooperative and confused." "The patient was unable to cooperate because of lethargy" (this was a patient with ammonia intoxication).

Of a patient dying of hepatic and renal failure we read, "Throughout his hospital stay the patient had displayed varying degrees of emotional lability and alertness. During the last 4 weeks of his life he had fluctuating periods of lethargy, drowsiness, obtundity, and disorientation." In a discussion of the treatment of pneumococcal pneumonia, the case descriptions of patients who unquestionably were delirious include, "He was irritable and thrashing about." "For the first 3 days the patient was restless and almost maniacal." "On admission he was semistuporous, and although responsive to questioning, his answers were irrational. Eight hours after admission he was afebrile, completely rational, and was able to sit up and eat his meals." A good example of a hodgepodge description is the statement, "The retention of carbon dioxide occurring in patients with alveolar hypoventilation may produce a variety of mental manifestations, i.e., depression, anxiety, marked irritability, somnolence, confusion, delirium, and coma." These examples are picked at random and are completely typical of current writing when the mental status of the patient is mentioned at all, which often it is not. It is apparent that most physicians have only the vaguest comprehension of the phenomena they are attempting to report and therefore dispose of the matter by referring to whatever most forcibly strikes
their attention, whether it be the significant process or not. This is clearly an unsatisfactory situation, hardly conducive to clear understanding of the conditions being reported. It might be compared to reports of examinations of the heart which read "There were unusual sounds," or, "There was an exceptionally fast and disturbed rhythm," or, "An odd pause every now and then," clearly tantalizing but unhelpful descriptions even if vaguely correct.

We have intentionally delayed discussing the clinical picture of delirium until the case had been developed for delirium as a unified syndrome, a syndrome of cerebral insufficiency. If we have achieved this, we hope it will now be possible for the reader to comprehend in an orderly and logical fashion the manifestations of delirium. Hopefully this should lead to more frequent recognition and more accurate description of delirium.

The distinctive feature of delirium concerns the cognitive functions and the level of awareness, ranging all the way from coma, the most severe degree, to a disturbance which is detectable only by very exacting (and clinically impractical) psychologic testing. That there is a degree of metabolic insufficiency beyond which consciousness cannot be maintained is a quantitative rather than a qualitative consideration, as evidenced by the fact that all the characteristics of delirium can clearly be demonstrated if the patient can be studied before he becomes comatose or during the period of recovery from coma.

The reader may perhaps best orient himself as to the nature of the experience of mild delirium by his own personal experience. That most familiar is mild alcoholic intoxication. Also similar, although not strictly speaking "delirium" as we have defined it, is the experience of being awakened suddenly in the middle of the night, especially in a strange place. Subjectively one notes a slight blurring or haziness of perceptions so that what impinges on the sense organs is not so promptly or accurately identified or apperceived. The familiar motion picture stunt of depicting the experience of the drunken person by a blurred image which only gradually comes into focus is a good but perhaps caricatured demonstration of this. Not only does one have difficulty in focusing attention on the important percept, but one also has difficulty in screening out interfering perceptions, whether they arise from the external environment or from within. Similarly one notes a difficulty in marshaling one's thoughts logically, coherently, and appropriately. Desired memories and associations seem less readily accessible and often undesired or inappropriate memories and associations appear in their place. The execution of appropriate behavior and speech encounters the same difficulties.

With very mild delirium, such difficulties may be quite inapparent to the observer since, for the most part, they can be adequately overcome by heightened effort. Nonetheless the EEG at this point already will show some slowing as we have demonstrated in both experimental and clinical delirium. But, if the patient does not or cannot mobilize the increased effort, the observant physician will note vagueness, uncertainty, hesitancy in the patient's manner of speaking, and errors or contradictions of fact that the patient may or may not himself correct. At this point the patient may acknowledge that he is having some difficulty in thinking or remembering.
With further advance of the delirium, this state becomes more manifest. Now the patient becomes unable to perform correctly, even with heightened effort. He begins to appear confused and even bewildered. His responses tend to be slow, uncertain, and often reveal errors in memory, retention, and recall. The heightened effort may be revealed by the knitted brow, the expression of concentration, the slowness of the responses, and a tendency to look up or look around when asked even relatively simple, straightforward questions. At this phase the patient is beginning to have significant difficulty in dealing with abstract concepts. One of the earliest expressions of this is the disturbance in time orientation, first in respect to the day of the week and later in respect to month and year. He shows increasing difficulty in retaining and grasping what is presented to him, so that he becomes less able to follow the directions of doctors, nurses, or family. He gives up reading because he cannot comprehend, retain what he reads, and his conversation becomes increasingly limited, coherent, and irrelevant.

Soon he manifests confusion in his orientation as to place, misidentifying his location, or identifying it correctly only by the most painstaking visual search to establish landmarks. He now may misidentify what he perceives, mistake voices in the hall for those of familiar persons or pieces of furniture for people. His language becomes less coherent and understandable, and his capacity to maintain attention for any type of task progressively becomes diminished. Concurrently there tends to be progressive loss of motor control and of skill with increasing difficulty in feeding, grooming, writing, etc. Incontinence of urine and feces, drooling, and spilling of food and water all are characteristic of more severe delirium. At first the patient may have the delusion that he is urinating or defecating in the proper place, as in a dream, and may feel guilty or ashamed later to discover that he had soiled his bed. As the condition deteriorates, however, the patient seems to lose all awareness of these social requirements, if he is aware of urinating or defecating at all.

In the final stages of delirium, before stupor or coma supervenes, the patient's speech usually becomes incoherent and muttering. He seems to be incapable of comprehending or responding to even the simplest questions, and he is totally disoriented for time and place. He may recognize only the most familiar persons in his life, often misidentifying strangers as members of the family. Picking, groping, grasping, and ataxic movements make their appearance. He becomes less and less responsive, lapsing into a stuporous state and finally into coma.

With each of these stages there is an increasing degree of slowing of the EEG. With the mildest degree of delirium the slowing may only be demonstrated by doing a frequency count, but as the disorder increases in severity the EEG becomes more obviously slow and irregular, reaching in progressive steps to a very irregular and slow (1 to 3 per second) pattern of coma. Usually when the slowing has reached 5 to 6 per second or less, the characteristic disruption of the pattern by opening the eyes is no longer observed, a physiologic correlate of the reduced impact of externally derived perceptions.

This description in essence summarizes the sequence of changes in the level of consciousness characteristic of progressing delirium. Needless to say, the rate...
and order in which such developments take place vary greatly from person to person. Thus one patient, following an overwhelming noxious stimulus, such as a severe head trauma, may become instantly comatose, and recovery may reverse the steps just described. In some patients the disturbance in consciousness may progress only to a mild or moderate degree, while in others it may fluctuate considerably, depending on variations in the severity of the underlying metabolic disturbance. In every case, however, the degree of slowing of the EEG correlates well with the degree of decrement in the level of consciousness as is manifest by the progressive changes described above.

This description adequately delineates the psychologic and behavioral changes that characterize all cases of delirium. It by no means, however, covers the full range of behavioral and psychologic aberration which may be noted in the course of delirium. These run the gamut of all varieties of psychopathology, and, in this respect, delirium may simulate any type of mental disorder, neurotic or psychotic. But, as will be discussed later, the presence of the disturbance in the level of awareness and the characteristic EEG changes provide the basis for differentiation of delirium from other psychopathologic entities. If we postulate that the effect of a cerebral metabolic derangement is to interfere with or damage mental processes or mechanisms in the reverse order in which they have been acquired (learned), then the polymorphous character of the clinical expressions of delirium become more understandable. In addition to interference with the systems whereby new and current stimuli are perceived and related to old experience, the systems that have to do with the recording in memory of such new experiences and their subsequent translation into appropriate thought and action are also affected. Further, the systems that have to do with the maintenance and focusing of attention seem to be particularly vulnerable. These are all functions of the ego, and one is justified in presuming that the ego is weakened as a consequence of this attack on its organic substrate.

This weakening of the ego is also manifest in the varieties of bizarre thoughts and fantasies which erupt into consciousness and in the primitive character of some of the defense mechanisms that may be used. With the more severe degrees of delirium, one sees a mental apparatus virtually stripped of all but the most primitive ego functions and barren of the social and cultural standards represented by the superego and the ego ideal. This means that, over and above the universal and characteristic disturbance in the level of awareness, the more personal and idiosyncratic characteristics of the behavior of the delirious patient will be determined by his own past development.

Accordingly, among delirious patients, we may expect to see varying degrees of anxiety, depending on the nature of past experience, the variety of ego defenses available, and the nature of support the patient receives from his environment. Some patients may experience a great deal of free-floating anxiety, with frightening thoughts, fantasies, and dreams and with all the behavioral and physiologic expressions of the anxiety reaction—tremor, sweating, tachycardia, and so on. Occasional patients succeed in overcoming this anxiety by denying or minimizing the extent of their intellectual defect, by withdrawing from or avoiding situations in which their defects may become manifest, by recourse
to sleep, or by confident dependence on the physician, nurse, or family who care for them. Patients with such successful ego defenses may reveal little if anything of their delirium by a façade of pleasantness, cooperativeness, or by parrying with humor or some aggression questions or tests which may expose their difficulty. Some patients with relatively well-developed and healthy ego function, however, may even lapse silently into coma with only a very attentive observer appreciating the development of delirium. At the other extreme are the minimally compensated patients, psychologically speaking, in whom the metabolic derangement applies the coup de grâce, so to speak, to the already weakened organism. Among such patients one is more likely to see extreme degrees of anxiety, panic, with gross sense deceptions, hallucinations, and delusions of a paranoid character. Such patients are so grossly disturbed that they rarely escape the physician's attention, even though the diagnosis of delirium is not always correctly made. The chronic alcoholic seems particularly vulnerable to this form of development, perhaps as much the result of being the kind of person who becomes a chronic alcoholic as the result of the prolonged influence of alcohol or withdrawal from it. Such patients may injure themselves in panicky fits or may injure others in frantic attempts to ward off what they misinterpret as attacks.

Equally important are the varieties and expressions of depression in a delirious patient. A patient who has previously experienced depression or a patient whose earlier development renders him more vulnerable to depression may well respond to the perception of loss of his intellectual and mental function with depression. Some patients may respond with excessive shame to the inability to maintain standards, especially in respect to soiling. And so patients may respond with guilt to the disturbing aggressive and sexual impulses which surge up during the delirium. Some of these patients present serious suicide risks and it is sometimes only the severity to the underlying disease which renders them physically incapable to carrying out the suicide.

All varieties of neurotic and psychotic behavior may become manifest and accentuated in the course of delirium. In general, such developments constitute accentuations of previous tendencies which may have been latent up to this time.

An important clinical characteristic of delirium is the fluctuation in its manifestations. Many patients appear to be much more manifestly disturbed and delirious at some periods of the 24 hours than others. Careful examination, including EEG study, reveals that these fluctuations generally are not related to changes in the underlying metabolic disturbance, but rather to psychosocial and environmental factors. Thus it is quite common for the delirious patient to appear more anxious and disturbed at night than during the day, a situation which finds its explanation in the fact that at night the patient has fewer sensory guides to help him in orientation. The darkness and the absence of familiar persons contribute to this. This accounts for the frequent report by doctors and nurses that a patient “suddenly became delirious” at night; most often the
patient already was delirious but did not manifest behavior that was recognized as disturbed until the additional stress of darkness brought forth more manifest anxiety and disturbed behavior.

THE EXAMINATION OF THE DELIRIOUS PATIENT

In the great majority of instances, the presence of delirium can be recognized and established in the course of taking the routine history. Once the physician becomes suspicious that there is a reduction in the level of consciousness, he can test this without the patient necessarily discovering that he is being so examined. For example, by repeating questions concerned with dates and names of places involved in the patient’s illness, he may discover whether or not the patient is able to give consistent answers. By asking the patient to provide such factual data as are usually found on the front sheet of a hospital record or are easily ascertained from other sources, as the home address, telephone number, date of birth, date of marriage, ages and dates of birth of children, physician’s name, address, and phone number, duration of residence, etc., it is usually relatively simple to demonstrate all but the milder degrees of disturbance in consciousness. The atmosphere of testing, which may be disturbing to some patients, may be eliminated if the physician simply frames his questions in terms of asking for information, even asking the patient for the date as if he, the physician, does not know it.

A number of relatively simple testing procedures are available if one wishes to establish the presence of a milder delirium or to follow serially the course of delirium. Perhaps the most useful is the serial subtraction of numbers, asking the patient to subtract 7 from 100 or 3 from 100 down to zero. Here one notes the speed, accuracy, the number and nature of the errors made and whether the patient perseverates or loses his place or simply errs in subtraction, or has to seek recourse to a concrete guide such as counting on his fingers. This procedure tests not only attention and concentration but also retention, memory, and the capacity to handle abstract concepts (numbers) without recourse to sensory guides. In evaluating this test, one must take into account the educational background and previous intellectual level of the patient. It cannot be used in patients who have not had at least a sixth grade education. Another useful procedure is to test the number of digits which the patient can retain and repeat forward or backward. The interpretation of familiar proverbs tests the capacity of the patient to deal with abstract concepts. With the more severe disturbances in consciousness, the patient may be unable to repeat the proverb accurately, much less interpret it. With somewhat less severe delirium, the patient may repeat the proverb in essentially the same terms, or give as its interpretation the concrete literal one. The increasing capacity to provide an abstract and generalized interpretation reflects improving function.

Other techniques of examination are described elsewhere.\textsuperscript{36,38}

THE DIFFERENTIAL DIAGNOSIS OF DELIRIUM

The possibility of delirium should be considered in any patient who is seriously ill organically. Among such patients, however, it must be differentiated from
varieties of apathy, withdrawal, depression, and anxiety which may accompany serious illness. These states, however, are not accompanied by the varieties of disturbances in the level of awareness which have just been described for delirium, and, if the patient’s cooperation can be gained, the absence of such disturbances becomes clearly evident on examination. When in doubt, the issue can always be settled by an EEG, although it must be appreciated that a single normal EEG does not necessarily rule our delirium since the premorbid record may have been faster. A repeat record after recovery will settle this.

**Dementia.**—The distinction between dementia and delirium is a somewhat arbitrary one, established by convention. Delirium has been defined as a reversible disturbance and dementia as an irreversible disturbance. Obviously, there are many situations in which one cannot know whether or not the condition is reversible until after a period of observation. Thus if the underlying disorder, be it an infection, heart failure, or whatever, clears up and there is significant improvement in either mental status or EEG, in all probability the condition was dementia and antedated the development of the more acute illness. More often, and especially in the older age group, we deal with patients with a pre-existing mild degree of dementia upon which is superimposed a further impairment in the course of the acute illness. In most instances, dementia develops either gradually over a matter of months or even years or very abruptly, following some major cerebral insult, such as a head injury or a stroke from which recovery does not take place. Because the condition is more stable and chronic, there is more opportunity in the demented person for the development of compensatory psychologic devices, the presence of which are of some value in differentiating dementia from delirium. For example, the demented person is somewhat less likely to manifest the extremes of anxiety or panic noted in some delirious patients, although he may show considerable lability of expression, affect, with irritability, easy laughing and crying, and variations between expansive and depressive moods. The extent of the intellectual defect is often obscured by the use of denial, perseveration, and confabulation. Old memories, usually pleasant or successful in fact or in fantasy, are repeated endlessly as part of a pattern of recapturing the more successful past and denying the more restricting present. The attempts of the examiner to test current performance may be rewarded by recourse to anecdotes and reminiscences. In general, the disturbance in retention, recent memory, and the capacity to use abstract concepts is less immediately obvious.

The EEG in dementia is less consistently slow as compared to that in delirium. Indeed a significant proportion of at least mildly to moderately demented patients have normal or borderline EEG’s. This is probably explained by the fact that the abnormally slow potentials are arising from damaged neurons. In dementia we may presume that the neurons have died or at least are no longer effectively functioning. The electrical activity arising from the neurons still present may not deviate significantly from the normal.¹⁹,⁴⁰

**Depression.**—Many depressed patients complain of difficulty in thinking and of memory loss. The general psychomotor retardation commonly accompanying depression may make it difficult to differentiate such manifestations from...
those commonly seen in delirium. When in doubt the matter can be easily settled by an EEG, since depression is unassociated with any EEG change.

Schizophrenia.—As mentioned previously, the psychotic manifestations in delirium may occasionally simulate those of schizophrenia. Ordinarily in schizophrenia, tests for orientation and level of awareness will indicate no defect. However, if the patient is mute or uncooperative, an EEG will provide the differentiation, since diffuse slowing of the EEG is not a finding in schizophrenia.

Hysteria.—The hysterical psychosis (including the Ganser syndrome, pseudodementia, and prison psychosis) may simulate delirium. In some cases the determinants for the choice of such manifestations were a true delirium in the past or identification with an important person who suffered from delirium. Clinical examination will usually readily distinguish hysterical psychosis from delirium. Generally the difficulties in memory, concentration, and other cognitive functions are either much too sweeping or are spotty. Thus a patient may manifest amnesia in many areas but excellent memory in others. Or the difficulty in intellectual performance may assume ludicrous proportions, such as being unable to answer correctly how many legs a three-legged stool has. Amnesia for one’s own identity is almost always a hysterical phenomenon, practically never occurring during delirium. The severely delirious persons may be unable to give his name, but he is not likely to complain of this fact. In any event, the diagnosis is again readily settle by the EEG, which will reveal no abnormality in hysteria.

Excitements.—Manic and schizophrenic excitement may present considerable difficulty in diagnosis and differentiation from delirium, especially since excited persons are likely to be overmedicated, producing a superimposed delirium. The problem is usually clarified after a brief period of clinical observation.

Drugs.—A variety of drugs such as mescaline, lysergic acid, quinacrine, and many others may produce acute psychologic disturbances which are different from delirium. In general these materials produce their effects probably by specific affinity for certain parts of the nervous system or even components of the neurons. They do not produce reductions in the level of consciousness, as we have defined this clinically, but rather certain types of heightened perception—sometimes with hyperalertness and sometimes with states of withdrawal. They are more likely to lead to excited states or states with vivid, complex visual or auditory hallucinations. While the patient may be preoccupied with such experiences, if one can secure the patient’s attention, it will be found that he has no significant defect in cognitive function. In contrast to the delirious patient, he may have very vivid memory of these experiences after the disorder is over. It is perhaps significant that the EEG during such states does not show diffuse slowing as in delirium, but rather either diffuse acceleration (quinacrine), sleep patterns in an alert state (atropine), or focal spikes or paroxysmal slow activity (mescaline). There are some grounds to suspect that delirium tremens, the more or less distinctive syndrome noted in alcoholics (which may be part of a withdrawal syndrome), has more in common with these states than with delirium, or at least is a mixture of the two. The basis for this suggestion is the prominence and consistency of hyperalertness, hypervigilance, and hallucinations in delirium.
tremens, the clarity of the patient’s memory of such experiences after recovery, and the relatively minor character of the EEG changes. Rather than showing diffuse slow activity, most patients with delirium tremens show low voltage fast or moderate voltage fast activity. We believe it was their emphasis on alcoholic patients which misled Victor and Adams to state that the EEG in delirium is usually normal.

**Sensory Deprivation.**—Experimentally, reduction in sensory input provokes certain psychologic disturbances of psychotic proportions even in some healthy individuals. Hallucinations and distortions of the body image are particularly prominent and may provoke severe anxiety. It is now becoming evident that some psychotic episodes occurring among patients in the respirator and with bandaged eyes are of this origin rather than due to cerebral insufficiency. Obviously both factors may operate. In any event, the EEG again will provide the differential since slowing does not occur as a part of the sensory deprivation syndrome.

**SUMMARY**

The thesis is presented that a derangement in the general functional metabolism of the brain underlies all instances of delirium and that this is reflected at the clinical level by a characteristic disturbance in cognitive functions and at the physiologic level by a characteristic generalized slowing of the electro-encephalogram. As background for this thesis are summarized the studies of a large number of patients exhibiting delirium in the setting of a wide variety of physiologic and biochemical derangements as well as instances of delirium experimentally induced by techniques known to affect cerebral metabolism adversely.

The clinical characteristics of delirium are carefully delineated and the basis established for the identification of delirium and its differentiation from other types of psychologic disturbance commonly seen in organically ill patients.

**REFERENCES**

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