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SURGICAL CONTRIBUTIONS TO PSYCHIATRIC TREATMENT

American Handbook of Psychiatry

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e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 5* edited by Silvano Arieti, Daniel X. Freedman, Jarl E. Dyrud

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Surgical Contributions To Psychiatric Treatment

Introduction

Viewed in historical perspective it is clear that surgical contributions to psychiatric treatment were developed parallel with advancing insight into how the brain "works." Since the 1930s surgical contributions fall into three distinct but overlapping epochs, representing successive levels of insight into the central mechanisms that govern emotion and behavioral activity.

During the first epoch which began in 1935, the surgical approach was entirely empirical. The objective was disconnection of a major portion of the anterior frontal lobe from the rest of the brain. Since no physiological function was then ascribed to the isolated regions, the procedures were referred to as "psycho" (mind) surgery.

Within ten years however, limitations of this empirical frontal-lobe lesion were apparent. During this period it was demonstrated in animal studies, and confirmed in man, that there were two discrete areas within the so-called "silent" zone of frontal disconnection from which strong autonomic responses could be elicited by electrical stimulation. This suggested that a more selective and physiological approach to surgical treatment might be developed.

By 1950, the empirical frontal transection of "psychosurgery" was being replaced by physiologically defined and anatomically limited lesions of the frontal lobe. With this advance the epoch of empirical "psychosurgery" drew rapidly to a close.

During the second epoch, attention focused on the anatomically restricted target areas of autonomic representation in the posterior orbital and anterior cingulate regions of the frontal lobe. Selective frontal lesions in these areas have proven to be clinically effective in alleviating otherwise intractable disorders of affect, but have not proven effective in modifying the schizophrenic psychoses which represent the major burdens of chronic psychiatric illness.

Clinical studies of temporal-lobe epilepsy have provided persuasive evidence that temporal-lobe circuits must be involved in many of the manifestations of the schizophrenialike psychoses. In addition, it has become increasingly clear that the central mechanisms governing visceral, emotional, and psychic activity are not arranged in separate and specific structural and functional packages, but rather as integrated circuits in a larger dynamic complex—the limbic system.

Thus, during the third and current epoch of surgical contribution to psychiatry, the frame of reference has extended beyond the frontal lobes to

encompass the more complex territories of the temporal-lobe and limbic system. Therapeutic strategies appropriate to the current "limbic" era of biological psychiatry are still developing.

In the following brief review we will trace the development of surgical contributions to psychiatry from an opening "empirical" phase to an increasingly refined physiological orientation; from a fixed focus concept to a balanced "systems" approach; and from an anatomically ablative to a functionally modulative methodology.

Empirical Frontal-Lobe Transection: "Psychosurgery"

The principal events leading to the development of surgical therapy for psychiatric illness are well known. In 1935, Fulton and Jacobsen (1935) presented to the International Congress of Neurology in London, observations on two now famous chimpanzees, *Becky* and *Lucy,* who were relieved of experimentally induced frustrational and neurosis-like behavior by extensive frontal-lobe ablation. Viewing the film records of this animal study, the Portuguese neuropsychiatrist, Egaz Moniz, visualized the striking changes in the animal's behavior in terms of specific psychiatric patients under his care. Together with his neurosurgical colleague, Almeida Lima, Moniz designed a surgical lesion which transected connections of the anterior frontal lobe with other parts of the brain (1936). This frontal lobotomy or leucotomy (cutting

of white matter) was considered functionally equivalent to the technically more formidable ablations carried out in the laboratory studies. This frontal disconnection produced striking improvement in some patients with previously intractable psychiatric disability (Moniz, 1936).

In America clinical interest in this empirical surgical approach to psychiatric therapy was stimulated by the monograph, *Psychosurgery,* by Freeman and Watts, published in 1942. This study presented clinical data on eighty surgically treated patients, and raised widespread expectations that this new mode of therapy might substantially reduce much of the individual and social burden of chronic psychiatric illness. With rapidly rising public interest and demand "psychosurgery" was widely undertaken.

Although the frontal disconnection resulting from the standard lesion of psychosurgery was frequently followed by strikingly beneficial changes in otherwise unremitting disability (Freeman, 1942; Grantham, 1951; Paul, 1956; Rylander, 1973; Tucker, 1961) some limitations of this extensive frontal transection soon became apparent (Delgado, 1961; Rylander, 1948). Although the negative effects following operation were often relatively minor in degree compared with the extent of clinical improvement, they sometimes constituted a serious and irreversible deficit. In 1948, Fulton (1949) expressed this concern in "an earnest plea for caution on the part of the neurosurgeon, lest, in the absence of basic physiological data, he unwittingly

do irremediable harm to human beings who might be benefitted by a far less radical operation than is now being performed."

Thus, although the potential value of frontal intervention had been established by the early results of the standard lobotomy procedure, further refinement was clearly needed, first to define the minimal anatomical lesion that would be clinically effective, and second to establish, if possible, some physiological rationale for the procedure.

It was soon established that a more limited lesion, interrupting only the medial frontal pathways (Fulton, 1948; Grantham, 1951; Paul, 1956), was as effective as the standard frontal transection, and carried much less risk of unwanted side effects. Pathological correlations (Beck, 1950) indicated that it was injury to connections of the frontal polar convexity that accounted for the principal blunting effects on personality and intellect. By 1952 it was established on the basis of clinical studies that frontal lesions limited to the cingulate (LeBeau, 1952; Livingston, 1951; Ward, 1948; Whitty, 1952) or orbital (Green, 1952; Scoville, 1949; Tow, 1953) areas of the frontal lobe were equally or more effective in relieving severe psychiatric disability than the earlier standard transection, and that these lesions could be applied with some degree of clinical selectivity particularly in the affective psychoses. Most important, this limited intervention carried a much lower risk of undesirable side effects than the more extensive lesions of psychosurgery. In 1951, Fulton

was able to state "in the light of information we now possess, I believe that the radical lobotomy as carried out by Freeman and Watts should be abandoned in favor of a more restricted lesion."

The evolution in concept and practice which made psychosurgery obsolete clearly reflected increasing insight into how the brain "works." Unfortunately, awareness of this orderly evolution from an empirical to a physiological rationale for surgical intervention was obscured by the dramatic introduction of chlorpromazine therapy (Delay, 1952). The almost immediate assumption that pharmacotherapy would provide the definitive solution for severe chronic psychiatric illness, produced a backlash of criticism directed not only at the empirical procedure of psychosurgery, but, in effect, at all types of surgical intervention.

Historically the period of surgical empiricism in psychiatric therapy was brief. Its limitations were recognized early, and through continued clinical and laboratory efforts a rational physiological approach to selective frontal-lobe surgery was rapidly established. In retrospect, it is clear that psychosurgery was only a brief initial step in the sequence of surgical contributions to psychiatric treatment.

Selective Frontal-Lobe Intervention

At the time that frontal lobotomy was introduced in America, all of the

territory anterior to the plane of section of the surgical lesion was regarded as physiologically "silent." Historically however, nearly fifty years earlier Spencer (1894) had demonstrated cardiovascular and respiratory responses from stimulation of the orbital frontal cortex in the cat, rabbit, dog, and monkey. Spencer's findings were confirmed by Bailey and Sweet in 1940, and by Livingston and his collaborators in Fulton's laboratory in 1947 (Livingston, 1947; Livingston, 1947). The possible clinical implications of these observations, however, were not discussed.

In 1945 Smith elicited a full range of autonomic responses from stimulation of the anterior cingulate gyrus in the monkey, and particularly noted that the responses "are those which are generally recognized as occurring in emotional expression, necessarily implicating this cortical region in the emotive process." See Figure 28-1.

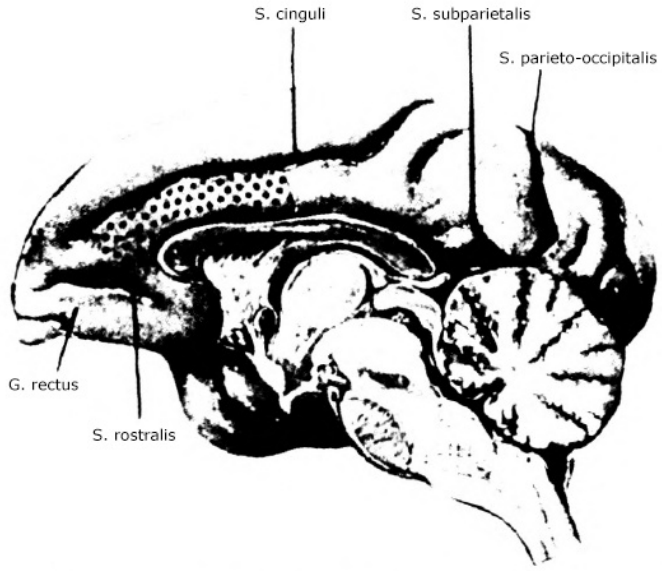
Two years later Ward (1948) confirmed Smith's observations, and stated that the most striking change following bilateral ablation of the cingulate gyrus in the monkey was a change in social behavior, characterized by a loss of fear and absence of aggression.

Thus, by 1947, on the basis of animal studies, the possible role of two powerful autonomic effector areas of the frontal lobe, in modifying emotional activity and behavior had been clearly established. Clinical application of

these experimental studies followed promptly.

In 1948 and 1949 clinical studies of selective lesions of the anterior cingulate gyrus were undertaken in England, France, and America. In 1951 and 1952, initial reports of these studies (LeBeau, 1952; Livingston, 1951; Whitty, 1952) showed that selective cingulate lesions were highly effective in relieving some patterns of previously intractable restless hyperactivity, irritability, excitement, anxiety, and obsessive compulsive behavior. With various types of cingulate disconnection there was little or no evidence of loss of intellect or blunting of personality.

Figure 28-1.



The medial surface of the brain of macaca mulatta showing the area of the anterior cingulate gyrus from which autonomic responses are elicited by electrical stimulation (Smith, 1945).

Concurrent studies of selective lesions of the orbital cortex and its underlying white matter (Green, 1952; Tow, 1953). demonstrated that disconnection of this area of autonomic representation is particularly effective in relieving the intractable depressive syndromes.

In physiological terms, the reduction of psychic and motor hyperactivity following cingulate disconnection suggests the removal of an overdriving facilitatory mechanism, while the release of psychic and motor activity

following orbital disconnection suggests the removal of overactive inhibitory mechanisms.

It is of interest that although direct electrical stimulation of these areas both in man and animals produces patterns of autonomic outflow that are quite similar, the response to ablation or disconnection in chronic psychiatric disorders is quite different. This suggests that although the final outlet pathways may be identical, the intermediate circuit relationships are unique. In ongoing activity one can visualize that constellations of neurones in the cingulate and orbital cortex exert a quite different tonic bias on the central mechanisms regulating the affective state. In this context "normalcy" of affect represents a dynamic balance between these and other circuits, while persistent imbalance is expressed as affective disorder. The anatomical basis for such a functional hypothesis has been described by Nauta (1958; 1971; 1973).

Since the 1950s, there has been no basic change in the surgical approach to the treatment of the affective disorders. There is now extensive documentation of the clinical effectiveness of lesions limited to the frontal areas of autonomic representation in modifying intractable affective disorders (Bailey, 1971; Ballantine, 1967; Brown, 1968; Columbia-Greystone Associates, 1949; Foltz, 1968; Kelley, 1973; Kim, 1973; LeBeau, 1952; Lewin, 1960; Lewin, 1961; Livingston, 1951). New stereotaxic methods have been

developed for lesion placement together with new techniques of lesion production using radio frequency (Ballantine, 1967; Brown, 1973; Brown, 1968; Foltz, 1968), cryogenic (Crow, 1963), and radioactive instrumentation (Knight, 1964). Open methods of surgical ablation or tract section under direct vision are less frequently employed, but the target areas remain essentially the same.

During this period, the conceptual framework within which surgical contributions to psychiatry were evolving had extended beyond the frontal lobes to include the more complex territories of the temporal-lobe and limbic system.

The transition from a frontal to limbic orientation has been facilitated by the fact that the patterns of limbic-system representation and the topography of autonomic projection in the frontal lobe are identical.

The Evolution of the Limbic-System Concept

The designation "limbic system" was first used in its current context by MacLean in 1952. The terminology was derived from Broca's description in 1878 (Broca, 1878) of "la grand lobe limbique" made up of the cingulate gyrus superiorly, and the hippocampal gyrus inferiorly, joined anteriorly beneath the genu of the corpus callosum by the "olfactory" lobe. These prominent structures on the medial wall of the hemisphere formed a "limbus"

or hem-like ring around the foramen of Munro at the point of lateral evagination of the embryonic neural canal from which the cerebral hemispheres develop.

The structures of Broca's limbic lobe were traditionally considered to be part of the rhinencephalon or smell-brain. In 1901, Ramón y Cajal challenged this assumption. "Since the memorable works of Broca, the general opinion has been that the limbic convolutions are the station for the distribution of primary and secondary olfactory fibers," but "all our efforts . . . persuade us that these conductors represent centrifugal or descending pathways passing near the olfactory centers, but that they have nothing more than neighborly relations with them." (Ramón y Cajal, 1955, pp. 117-118).

In 1933, Herrick made the suggestion that these "olfactory parts of the cerebral cortex" might be components of a nonspecific arousal mechanism for all cortical activity.

Shortly thereafter, Papez (1959) posed the question "Is emotion a magic product or is it a physiological process?" He answered by postulating that the structures of Broca's limbic lobe are part of a "harmonious central mechanism of emotion." Papez included not only the cingulate gyrus and hippocampus but their interconnections with the hypothalamic and anterior thalamic nuclei as well (see Figure 28-2). Although these structures of the *Papez circuit*

constitute only the medial components of what we now visualize as the *limbic system*, the basic relationships, which Papez postulated in 1937, have required little modification in subsequent years.

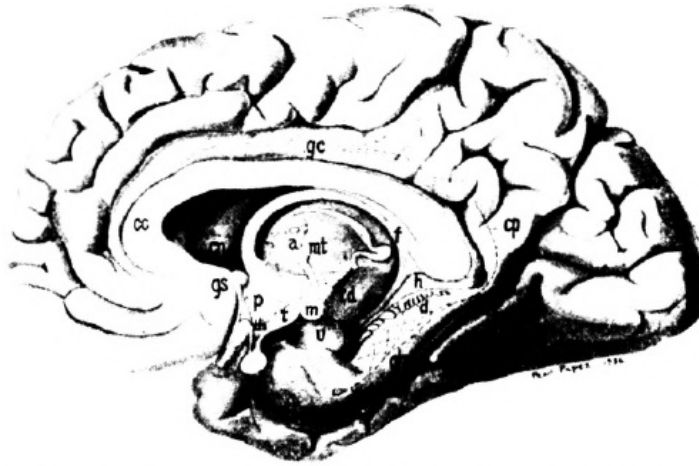
The first direct evidence providing physiological support for the Papez postulate came in 1945, when Smith demonstrated that a full spectrum of autonomic responses could be elicited by stimulation of the anterior cingulate gyrus in the monkey. It was pointed out that this display of pupillary, cardiovascular, respiratory, and pilomotor response was identical with that accompanying states of emotional activation in the intact animal.

Similar autonomic representation had been demonstrated earlier (Bailey, 1940; Livingston, 1947; Livingston, 1947) in the orbital frontal cortex, an area not included in the Papez "central mechanism of emotion."

Evidence that these two discrete areas of the frontal lobe exert modulatory control over patterns of autonomic outflow from lower brain-stem centers provided the basic physiological rationale for selective surgical intervention in the therapy of some patterns of affective psychiatric illness. The elaborate interplay between autonomic activity and all forms of emotion and behavior requires that the central regulatory mechanisms serving internally expressed (visceral) behavior, and externally expressed (emotional) behavior, be fully integrated at higher levels.

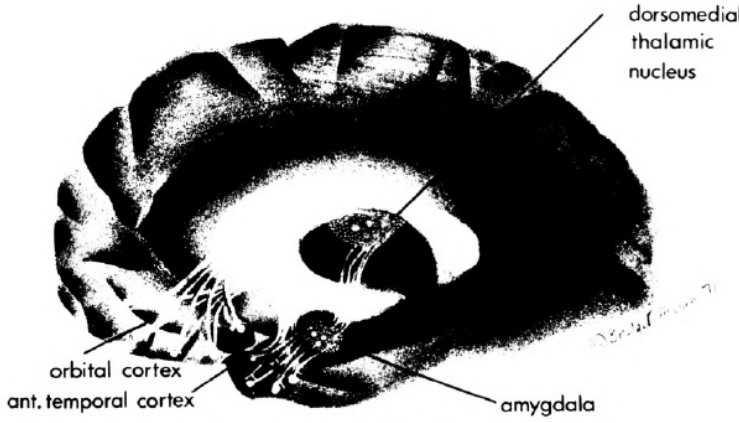
In 1948, Yakovlev extended the Papez concept to include a major group of basolateral mesopallial structures, i.e., the orbital, insular, and anterior temporal cortical areas, together with their interconnections with the amygdala and dorsomedial nucleus of the thalamus (see Figure 28-3). Within this circuit, the orbital cortex might play a role in the regulation of autonomic-emotional interaction parallel to that of the cingulate cortex in the Papez circuit. Although the patterns of autonomic response elicited by electrical stimulation of the cingulate and orbital frontal cortex are similar, indicating that they act on the same motor outflow pathways, the intermediate connections are strikingly different.

Figure 28-2.



The medial surface of the right cerebral hemisphere showing the principal structures included in Papez "central mechanism of emotion" (Papez, 1937) (Copyright 1937, American Medical Association.)

Figure 28-3.



The basolateral limbic circuit.

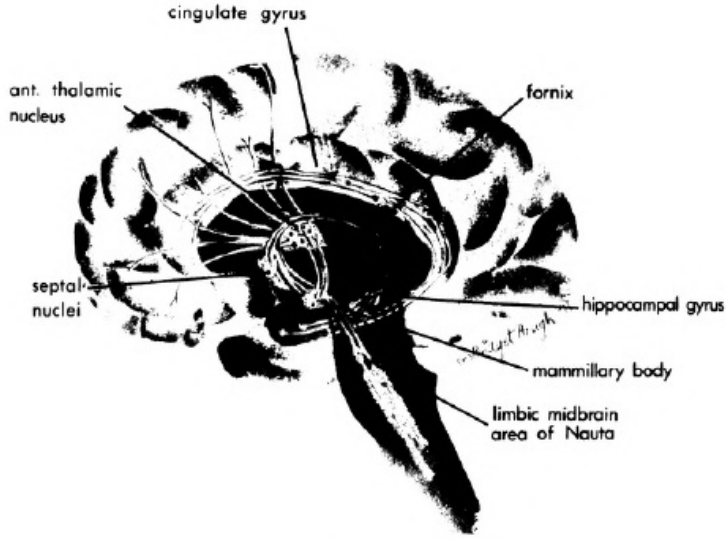
In 1952, MacLean proposed that the structures of the medially oriented circuit described by Papez (1937), and the basolaterally oriented circuit added by Yakovlev (1948) be given the common designation "limbic system."

The basic relationships, as defined in 1952, have been fully confirmed by subsequent studies. There has been increasing emphasis on the major linkage of the medial circuit with the reticular core of the brain stem (see Figure 28-4). Fibers from the great fornix bundle pathway are distributed widely from the septal preoptic level throughout the length of the hypothalamus to the limbic-midbrain area of Nauta in the tegmentum (1958; 1960; 1971; 1973).

If the medial limbic circuit were to be characterized in terms of this

prominent anatomical orientation, it might be said that the medial circuit listens to and interacts particularly with the reticular core of the brain stem. Through these pathways the medial limbic circuit receives the major input from the internal (visceral) world, and from the mechanisms of alerting and attention represented in the reticular activating apparatus of the brain stem (Chute, 1973; Livingston, 1969; Livingston, 1973; Livingston, 1973; Nauta, 1971; Nauta, 1973; Powell, 1973).

Figure 28-4.



The medial limbic circuit.

Clinical experience indicates that destructive lesions of structures

within this medial limbic circuit are characterized principally as states of motor and psychic hypoactivity, in effect a "turning off" of activating mechanisms. Clinical syndromes of apathy, akinesia, and mutism are seen with a variety of lesions (tumor, aneurysm, trauma, etc.) at all levels of this circuit from the medial frontal cortex to the midbrain tegmentum. Conversely, irritative disturbance within this circuit can be visualized as producing motor and psychic hyperactivity, i.e., an excessive driving of alerting and activating mechanisms. Syndromes of restlessness, irritability, excitement, anxiety, obsessive-compulsive behavior, etc., fall in this category. This type of clinical disturbance is most likely to be benefitted by selective lesions of the cingulate and medial frontal areas.

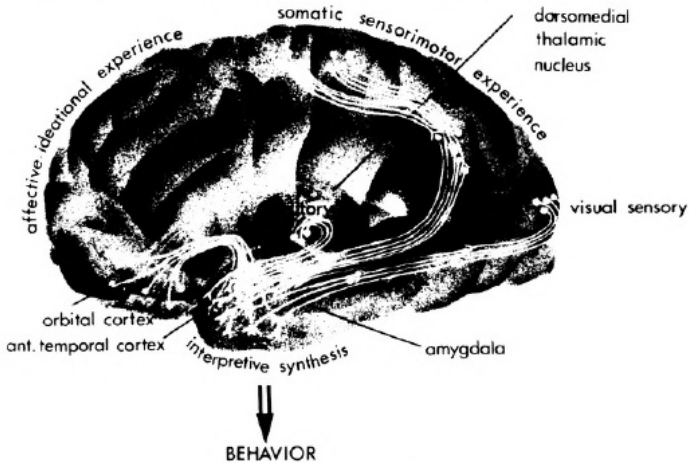
In contrast to the medial circuit, the baso-lateral limbic circuit receives its major volume of input from the great sensory receiving and association areas of the neocortex via pathways which converge in parallel on the transitional cortex of the anterior temporal lobe (see Figure 28-5). This circuit then appears to be listening particularly to sensory information from the body surface and the outer world. The disorganization of normal activity in this limbic sector, can be visualized as producing misinterpretation of sensory information from the body surface and from the environment, leading to the complex delusional systems, patterns of hallucination, and thought disorder that characterize the schizophrenic psychoses (Clemente, 1973; Powell, 1973).

If the dysfunctions that characterize the schizophrenic psychoses involve particularly temporal-limbic circuits, what evidence is available as to the effects of temporal-lobe lesions in these major psychiatric disorders?

Temporal-Lobe Lesions

The role of temporal-lobe surgery in the management of the major psychoses is not yet defined. Clinical information is largely indirect, since up to the present time most temporal-lobe intervention has been focused on the problems of epilepsy and pathological aggression.

Figure 28-5.



Convergence of information from neocortical sensory receiving and association areas on the limbic cortex of the anterior temporal lobe.

Temporal-lobe epilepsy is of particular interest since many of its manifestations suggest a transient psychosis-like dysfunction (Flor-Henry, 1969; Flor-Henry, 1972; Flor-Henry, 1973). During an attack the patient may appear detached from reality, have hallucinatory sensory experience (olfactory, visual, auditory, somatic, etc.), often with a strong emotional content, and may carry out complex psychomotor performance for which there is no subsequent memory (Geschwind, 1965). This miniature "psychosis" is commonly time-locked to the period of electrographic seizure discharge (Beard, 1963; Flor-Henry, 1969; Flor-Henry, 1969; Glithero, 1963; Smocygnsky, 1972). Of greatest interest, however, is the fact that with longstanding temporal-lobe epilepsy there is increasingly frequent interictal psychiatric disturbance extending from a mild change in personality to gross and continuous manifestations of psychosis. At this end point, the psychiatric characteristics of the "organic" psychosis associated with epilepsy may be indistinguishable from the "idiopathic" psychosis (Beard, 1963; Glithero, 1963). The clinical association between the seizure disorder and the complex psychic phenomena is accepted, but the extent to which they share a common pathophysiological substrate has not been established (Flor-Henry, 1969).

If the seizures and the schizophrenialike psychosis in temporal-lobe epilepsy are expressions of focal dysfunction in a common substrate, unilateral temporal lobectomy in patients with a well defined seizure focus should be followed by parallel improvement in the psychotic as well as

epileptic manifestations. Unfortunately this has not proven to be the case. Indirect benefits do occur as a result of improved social function in individuals who are free of seizures, but the basic characteristics of the psychotic disorder are not changed. As Falconer (1973) has stated, "the psychosis persists, although mellowed."

On the basis of clinical experiences and considerable experimental evidence it seems likely that the mechanisms responsible for the psychoses are multicentric and seldom dependent on the surgically resectable structures of a single temporal lobe.

What clinical information is available as to the effects of bilateral lesions in the temporal-limbic circuits?

Most of the relevant clinical data in this area are derived from the study of patients showing recurrent unprovoked aggressive behavior. The surgical approach utilized in most of the latter cases has been bilateral stereo-toxic lesioning of the amygdala. The initial studies by Narabayashi (1963) were carried out on individuals with extensive brain damage or severe impairment from longstanding intractable epilepsy. Here the operation had a marked quieting effect on behavior. In patients with no other evidence of brain defect than the seizure disorder and the unprovoked aggressive behavior, bilateral lesions of the amygdala consistently reduce emotional tension and affective

response (Mark, 1973; Nádvorník, 1973; Vaernet, 1972). Although these patients are emotionally more stable and function better socially, there is flattening of normal emotional responsiveness, together with decreased spontaneity and productivity.

Vaernet (1972) carried out bilateral amygdalotomies in a series of twenty schizophrenic patients, all of whom had had bilateral frontal lobotomy between ten and fifteen years earlier, but continued to be violently aggressive. Following amygdalotomy all of these patients were improved in terms of their aggressive behavior but their psychoses were not altered. They were described as quiet and generally cooperative but still deeply schizophrenic, in poor contact, and hallucinating.

The conclusion from clinical experience with bilateral amygdalotomy must be that this surgical lesion does not significantly alter the mechanisms responsible for the schizophrenias. Similarly, the combination of bilateral amygdalotomy with basolateral frontal tractotomy (Vaernet, 1972) apparently fails to relieve the schizophrenic syndromes. In addition, earlier evidence established the fact, that bilateral lesions of the hippocampus are not acceptable since they impose a disabling defect in memory (Milner, 1958).

Focal hypothalamic lesions have been shown to have a general "sedative" effect on some patterns of hyperactive behavior (Sano, 1966) and,

in combination with thalamic lesions, to modify some patterns of abnormal sexual behavior (Roeder, 1972).

Multiple lesions of the thalamus (Dynes, 1949) and combinations of hypothalamic, thalamic, and amygdala lesion (LeBeau, 1952) also modify behavior, but none of the changes described suggest that such lesions would be effective in the treatment of the schizophrenic psychoses.

Can other lesions or combinations of lesions in the temporal lobe and limbic circuits effectively modify the schizophrenic psychoses without imposing serious deficit?

At present there is little clinical evidence on which to base an answer to this question. Limited experience of Turner (1963), Brown (1973), and Crow (1963) suggests that in some carefully selected cases multifocal destructive lesions may be effective in relieving schizophrenic symptoms, but the data are insufficient to permit any conclusion regarding the applicability of such surgical intervention in the general therapeutic management of major schizophrenic illness.

Thus, although it is established that the affective components of intractable psychiatric illness can be benefited by precise and limited surgical intervention, no comparable formula for the treatment of the schizophrenic syndromes has yet emerged. Since schizophrenic illness reflects a much more

profound and extensive disorder of emotional, psychic, and behavioral activity than the imbalances of the affective disorders, it is quite possible that no type of ablative intervention will substantially relieve the disorder without sacrificing essential qualities of intellect, motivation, and personality.

There is now very good evidence to suggest that new nonablative approaches to the treatment of the major psychoses may prove fruitful in the future.

The Future Outlook

The most desirable approach to therapy of the major psychoses would be through nondestructive manipulations which could, over a period of time, permit the central mechanisms of emotional-behavioral control to return to a state of "normal" homeostatic balance.

If the schizophrenic syndromes reflect biochemical as well as neurophysiological imbalances, various noninvasive manipulations may be employed to modify the abnormal activity. This general approach to therapy is exemplified by the long established use of physical (EST) and pharmacological (phenothiazine) modes of therapy. The potential effectiveness of this approach increases dramatically with growing insight into the basic chemistry and physiology of brain function. This is illustrated by the striking improvement in the clinical management of Parkinson's

disease following the discovery of the role of dopamine in the nigrostriatal pathway (Hornykiewicz, 1973). Similar investigations of serotonin, dopamine, noradrenaline, acetylcholine, and other putative neurotransmitters, may produce equally dramatic breakthroughs in psychiatric therapy (Axelrod, 1974; Margules, 1972; Schildkraut, 1967; Smythies, 1973; Snyder, 1974). Some of the ultimate therapeutic possibilities from this rapidly expanding field of investigation, have been suggested in important reviews by Axelrod (1974) and Snyder, et al (1974).

Some biochemical and pharmacological measures may be applied systemically by oral and parenteral routes, but counterbalancing peripheral and central effects, together with problems of blood brain barrier, differential actions of the same agent in different parts of the nervous system, and dosage requirements for whole body administration may seriously restrict the use and effectiveness of potentially valuable agents. It is now possible, using stereotactic techniques for both electrophysiological and biochemical interventions to be direct to specific targets, and applied with precise control of timing and intensity.

The possibility of selectively changing the balance of activity in specific limbic circuits by introducing different patterns of facilitatory or inhibitory input, without imposing a "lesion," may open new avenues to effective therapy. Clinical information in this area is still very limited. Repeated low-

intensity electrical stimulation of particular limbic loci has been given some clinical trial (Heath, 1960), but has not yet produced lasting benefit. It is now possible to implant permanent receivers that will deliver patterned electrical stimulation to such electrode sites, using apparatus comparable to cardiac pacemaker systems. However, such electrophysiological techniques should be applied with considerable caution since there is substantial experimental evidence (Delgado, 1961; Goddard, 1969; Morrell, 1969; Racine, 1969) suggesting that repeated stimulation of limbic and neocortical structures may induce widespread changes in threshold and may establish a persisting "mirror focus."

Controlled biochemical intervention may carry less risk and offer greater potential for benefit. Some bits of relevant information are available. More than twenty years ago, as a screening test for patients under consideration for frontal lobotomy, Van Wagenen carried out direct infiltration of procaine hydrochloride into the white matter of the frontal lobe through frontal burr holes in a series of twenty chronic schizophrenic patients (1952). A striking reduction in psychic symptoms occurred in thirteen of the twenty patients, lasting in several cases for twenty-four to forty-eight hours, and in one case, after a second injection, persisting for two weeks, although the drug is completely hydrolysed in brain tissue and plasma in less than thirty minutes (Bailey, 1952; Livingston, 1972). In many of these cases the qualitative as well as the quantitative change in long-standing

schizophrenic symptoms and behavior was remarkable. More recently, Bucci reported using procaine systemically as a monamine oxidase inhibitor in a series of twenty patients with chronic schizophrenia (Bucci, 1973). In sixteen of the twenty cases there was a well defined sequence of clinical improvement over a period of six months. In four cases the drug had to be discontinued early because of aggravation of psychotic symptoms. These observations suggest that significant modification of the schizophrenic syndromes may be possible by using nondestructive biochemical and pharmacological modes of therapy.

Recent evidence from our experimental laboratory (Racine, 1975) suggests that there may be a definable electrophysiological basis for such changes in the emotional-behavioral state. In the kindling model of temporal-lobe epilepsy induced by repeated low-intensity stimulation of the amygdala, there is a progressive buildup of after-discharge which spreads widely throughout the limbic structures before overflowing into the motor pathways as a convulsive seizure (Goddard, 1973; Goddard, 1969; Racine, 1969; Racine, 1969). Once established, the pattern of seizure response to the amygdalar stimulus is stable over long periods (Goddard, 1973; Racine, 1972). In rat-killing cats, concurrent with the appearance of motor seizures, there is a striking and long-lasting change in predatory behavior (Adamec, 1974). This provides a useful model to study the electrographic correlates of limbic-induced motor seizure and behavioral change, and their modification by

various pharmacological and biochemical agents (Racine, 1969).

In recent studies (Racine, 1969) it has been shown that procaine administered systemically facilitates after-discharge in the limbic structures but has an opposite, inhibitory, effect on electrical excitability at the cortical level. In the same study, diazepam (valium) was found to have a strikingly suppressant effect on limbic excitability, but little effect at the cortical level. Diphenyhydantoin (dilantin) had effects very similar to procaine, i.e., blocking discharge at the cortex, but facilitating discharge in the limbic structures. Such well-defined and selective inhibition or facilitation of electrical excitability in different cortical and limbic loci raises the possibility of therapeutic modulation of central dysfunction in some of the psychotic states. Other drugs may have equally or more selective effects, and can perhaps be used in various combinations to suppress some of the physiological dysfunction underlying the schizophrenic syndromes. Specific transmitter substances may be utilized in a similar manner, systemically or by more precise presentation to particular loci, using stereotactic techniques for placement and fine implanted canula-reservoir systems for delivery.

The possibility of modifying disordered limbic activity and restoring a more normal cortico-limbic balance through nondestructive inhibitory or facilitatory biochemical "tuning" opens new avenues to therapy for the major psychoses.

Much additional important information will be forthcoming from many laboratories working at both basic science and clinical levels. The final therapeutic assessments must be clinical since there is as yet no adequate experimental model for chronic schizophrenia. The initial clinical trials must be carried out under the most thoughtful and careful scientific control, with reference to all of the social and legal restraints relating to clinical research and informed consent.

Although no therapeutic "formula" can yet be defined, there is reason to hope that the massive problem of the schizophrenic psychoses will not remain forever totally impregnable, and that through increasingly close collaboration with the basic neurosciences, surgical approaches will contribute to the breaching of its walls.

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