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Clinical and Electroencephalogram Investigation on Largactil in Psychosis (Preliminary Study)

1. Experimental investigations have been carried out with Largactil on chronic and acute mental patients.
2. The over-all improvement in chronic cases was 69 per cent. and in acute cases 60 per cent.
3. However, the transitory effects in acute cases indicate that while Largactil is extremely valuable in chronic psychosis, in acute psychotic breakdowns, it has value only as a sedative.
4. Electroencephalogram investigations showed that Largactil markedly decreases the muscle artefacts, decreases the frequency, and increases the voltage, causing a mild progressive synchronization and, in epileptics, it lessens the convulsive threshold.
5. In spastics it decreases spasticity through intravenous route, as tested by electromyogram.

(Author's Abstr.)

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How Brain Lesions Affect Normal and Neurotic Behavior. An Experimental Approach

Over a period of 6 years 50 cats and 40 monkeys were closely observed for (1) their individual and social characteristics; (2) their capacity to learn various skills; and (3) the form and persistence of the experimental neuroses induced in 23 cats and 18 monkeys by exposure

to adaptational conflicts. The animals were then subjected severally to lesions of the anterior or mediadorsal thalamus, the amygdalae, or cerebral areas 13, 23, or 24. The results to date indicate that the general and specific effects of cerebral lesions vary not only with their site and extent but also with (1) the pre-operative experiences of each animal and (2) its post-operative care and re-training. (Authors' Abstr.)

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The Conduction of Pain Above the Level of the Thalamus Opticus

The case is described of a 52-year-old man who, after a vascular accident, showed "thalamic" pain and hyperpathia of the left half of the body, this being so intense that it finally led to suicide. It was noteworthy that pain and thermal sensations were distinctly disturbed on the left, whereas the proprioceptive sensibility was completely intact. At autopsy a complex of small confluent foci of softening was found in the cortex and the medulla of the right parietal operculum and in the cortex of the insula. A retrograde degenerated fiber bundle could be traced via the posterior part of the internal capsule into the posteroventral nucleus of the thalamus, where a marked cellular loss had occurred. A distinct hypalgesia likewise existed in the second case, that of a circumscribed tumor, which had originated in the external capsule and led to demyelination of the medullary radiation to the parietal operculum. In the third case, that of a superficial focus of softening in the lower parietal gyri and the parietal operculum, a very marked disturbance in pain sensibility was found established in the crossed body-half, excluding the leg. In the discussion, attention is drawn to an observation by Déjerine and to the anatomical findings in the syndrome of pain asymbolia. Finally, it is pointed out that the so-called secondary sensory area, defined in man by Penfield, probably corresponds to the area which in the first clinicoanatomical observations may be considered as lost. It is accepted as a working hypothesis that at this site, and not in the posterior central gyrus, conscious pain sensation is established. (Author's Abstr.)

Regional Differences in Seizure Susceptibility in Monkey Cortex

Experiments were performed on eight monkeys in order to investigate the capacity of different cortical regions to initiate spreading seizure discharge upon direct stimulation.

It was found that the "epileptogenic" cortical zones were located in portions of the motor and premotor cortex, posterior cingulate region, superior temporal gyrus and tip, and parietal area. Other surface areas displayed little or no propensity to develop spreading after-discharge.

In these experiments, the subcortical nuclei most commonly involved in the cortically induced seizures were the reticular formation, septal region, and amygdala.

An inherent tendency of cells in the described cortical loci to respond to local stimulation by exhibiting after-discharge, and their functional relations with subcortical nuclei known to exert diffuse influences upon the central nervous system, may both be important factors in the initiation and spread of seizures.

(Authors' Abstr.)

A Psychiatric Study of Attempted Suicide in Persons Over Sixty Years of Age

Nineteen patients aged 60 and over were interviewed and examined immediately following a suicide attempt. These 19 patients were part of a larger study of 109 patients who had attempted suicide.

Every one of the 19 older patients had a clinically diagnosable illness. There were nine patients with a psychotic depression, five with a chronic brain syndrome (dementia), three with an acute brain syndrome (toxic psychosis), and two with chronic alcoholism. Thus, 89 per cent. of these patients had a psychotic illness. These findings concerning diagnosis contrasted with those in the younger group, aged 59 and under.

The majority of the suicide attempts in the elderly patients were serious (genuine).

Most of these patients suffered from a treatable (psychotic depression) or reversible (acute brain syndrome) disease. Therefore, many of them can be returned to society as useful citizens if a subsequently successful suicide is prevented.

The immediate management of these patients consists of hospitalization in order to treat the underlying illness and to prevent a successful suicide.

A follow-up study of 23 months showed that two patients, one of whom had a psychotic depression and the other an acute brain syndrome, had committed suicide.

(Authors' Abstr.)

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Pharmacotherapeutic Evaluation and the Psychiatric Setting

Data are presented illustrating the effects of chlorpromazine and reserpine prescription to patients at the Institute of Psychosomatic and Psychiatric Research and Training of the Michael Reese Hospital. The results have been less positive than most studies reported elsewhere. An attempt is made to analyze factors in the specific psychiatric setting and patient population that might account for these findings. One factor appeared to be the relatively negative attitude of our hospital personnel toward the prescription of drugs as compared with alternative modes of therapy. This attitude seemed to be the antithesis of enthusiasm regarding drug effects seen elsewhere. "Double-blind" studies of drug effects do not entirely preclude the communication of such attitudes, especially when "active drugs" are compared with relatively inert preparations.

The author concludes that the social context within which pharmacotherapy is undertaken has importance in the over-all evaluation of therapeutic effect. It appeared as relevant as the specific pharmacological action of the drug and the psychodynamic meaning to the patient of receiving the drug. An attempt has been made to explore some of the implications of these conclusions for evaluation of results in other psychiatric therapies.

(Authors' Abstr.)

Neurophysiologic Effects of Electrically Induced Convulsions

Neurophysiologic studies, utilizing a modified spectrochemical technique for following the distribution of cocaine used as a tracer agent, have been performed on cats under control conditions and after a series of electroshocks. The object of these experiments was to determine whether or not alterations in the concentration of cocaine occurred in the central nervous system after a series of electrically induced convulsions. Significant and relatively persistent rises in the concentration of cocaine were found in the cerebral cortex after repeated electroshocks which induced convulsions. Since no change was observed in the concentration of

cocaine in the blood of these same animals after electroshock, it was concluded that a series of electrically induced convulsions increased the permeability of the blood-brain barrier.

Gross changes in the electroencephalogram were observed to accompany the persistent change in the permeability, suggesting that cerebrovascular permeability may be important in the neurophysiologic conditioning of the brain.

The concept of cerebral neurophysiologic conditioning secondary to cerebrovascular permeability changes is discussed as possibly offering an explanation for persistent effects which might correlate with the clinical benefits of electroshock therapy. A review of the numerous other studies on electroshock therapy failed to show persistent neurophysiologic changes which could be correlated satisfactorily with the clinical effects of this form of therapy. The concept of cerebrovascular permeability is attractive in that (a) it involves a basic neurophysiologic mechanism capable of conditioning the neurophysiology of the central nervous system; (b) as demonstrated in the present study, this mechanism may be modified over relatively prolonged periods by electrically induced convulsions and hence might produce neurophysiologic effects that could be correlated with the somewhat sustained clinical benefits of electroshock therapy; and (c) although neurophysiologic processes, directly or primarily involving neuronal elements and pathways, could scarcely be expected from what is known of them to produce persistent effects, the mechanism considered has the advantage of offering an explanation for a sustained conditioning of these elements without itself being dependent upon them.

This thesis, however, cannot be accepted without further correlative studies, as indicated. (Authors' Abstr.)

Autonomic Pharmacology in Schizophrenia

In an attempt to elicit differences between the functioning of the autonomic nervous systems in schizophrenics and in nonschizophrenics, small, carefully selected samples from each group were subjected to several pharmacodynamic investigations. Both a sympathomimetic agent (synthetic 1-epinephrine) and a parasympathomimetic one (methacholine (Mecholyl)) were employed alone, and together with their respective blocking agents (phentolamine (Regitine) and atropine). The sympatholytic (phentolamine) and parasympatholytic (atropine) agents were then employed independently. Advantage was also taken of the nicotinic action of carbachol in atropinized subjects to produce pharmacologically induced sympathetic discharges.

The rationale for using pharmacological agents to study autonomic physiology is stated; the literature on the use of autonomic drugs in schizophrenics is reviewed, and an attempt is made to explain some of the reported conflicting results of previous investigators.

The results of the present study are not striking. The diminished reactivity of schizophrenics to injected epinephrine described by a majority of authors and the results of Hoffer's atropine test could not be confirmed. A definite tendency toward differences between the responses of diastolic pressure of the schizophrenic and the nonschizophrenic groups to phentolamine was elicited, and a possible tendency toward differences between the groups as a result of the pharmacologically induced sympathetic discharge was noted. As several previous studies have shown, the schizophrenic reaction is characterized by greater variability and slower homeostatic mechanisms than is that of the control group.

The literature indicating the importance of the autonomic nervous system (with emphasis on its pharmacodynamic aspects) in many of the current biological-psychiatric studies of schizophrenia is reviewed. The usefulness of pharmacological methods of study is restated, and plans for further investigation are presented.

(Authors' Abstr.)

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An Objective Test which Differentiates Between Neurotic and Psychotic Depression

The sedation threshold is an objective determination based upon the EEG and speech changes induced by intravenous amobarbital sodium. The main purpose of this study was to apply this test to the study of depressive states, particularly to the problem of distinguishing between neurotic and psychotic depression. Additional purposes were to obtain data concern-

ing (a) neurophysiological differences between anxiety and depression and (b) the relationship between the sedation threshold and the effects of electroconvulsive therapy (E.C.T.).

Sedation thresholds were determined for 182 patients in the following diagnostic categories: psychotic depression, schizoaffective psychosis with depression, "hysterical" depression, neurotic depression, and anxiety state.

Results were as follows: (a) Sedation thresholds of patients with neurotic and psychotic depressions were markedly different; the test differentiated between these groups with about 95 per cent. accuracy. Age difference was not an influential factor. Thresholds were low in psychotic depression, regardless of the degree of agitation or history of previous depressive episodes. (b) The thresholds of patients with anxiety states were similar to those of patients with neurotic depressions and almost always higher than those of patients with psychotic depressions. (c) Patients with high sedation thresholds (neurotic depressions and anxiety states) were treated with (E.C.T.) much less frequently than patients with low sedation thresholds (psychotic and "hysterical" depressions). When (E.C.T.) was given, the short-term therapeutic response of the high-threshold patients was significantly poorer than that of the low-threshold group. (d) The sedation thresholds of psychotic depressive patients who had received (E.C.T.) prior to testing were higher than those of patients not recently receiving such treatment.

The following conclusions were reached: (a) The sedation threshold appears to be a valid objective method for the differential diagnosis of depressive states. (b) The results supported the validity of the concept which distinguishes between neurotic and psychotic depressions. (c) The relationship between the sedation threshold and depression was probably secondary to the effect of another factor, degree of impairment of ego functioning, on the threshold. (d) The sedation threshold appears to have some validity for predicting the outcome of E.C.T. (Authors' Abstr.)

The "Protein Profile" in Disorders of the Central Nervous System

The protein fractions in serum and cerebrospinal fluid (C.S.F.) of 115 patients with neurological diseases, other than typical multiple sclerosis (M.S.), and of 9 debilitated patients with non-neurological disorders were studied.

The neurological cases, for statistical purposes, were classified according to their predominant pathologic lesion, as far as this could be estimated clinically, into five groups. This classification was based on whether the disease was clinically stationary or whether it was suggestive of progression with respect to destruction of myelinated structures and/or nerve cells.

The combined protein changes, termed the "protein profile", were compared by means of group statistics with those of a group of patients with typical multiple sclerosis and with those for a group of normal subjects.

The results demonstrate that the chemical (C.S.F.) protein values, confined to γ -globulin and total protein (T.P.) determinations, differ from those for typical multiple sclerosis in a large spectrum of neurological disorders, which includes cerebral palsy, Parkinsonism, amyotrophic lateral sclerosis, syringomyelia, familial and nonfamilial degenerative diseases of the central nervous system, atypical multiple sclerosis, posterolateral degeneration with pernicious anemia, Schilder's disease, primary lateral sclerosis, residual paralytic poliomyelitis, etc.

There was considerable overlapping in the ranges of the electrophoretic serum protein fractions in all the groups of neurological patients with multiple sclerosis except for cases with evidence of stationary cell loss, such as patients with residuals of paralytic poliomyelitis and cerebral palsy, as well as for a group which included patients with posterolateral degeneration with pernicious anemia, Schilder's disease, and posterolateral sclerosis of unknown etiology. Only the series of patients with hemiplegia showed an overlapping of the protein profile with that for typical multiple sclerosis, regardless of the duration of the disease.

A control group of debilitated patients, with and without neurological disorders, displayed overlapping serum protein findings with the (M.S.) group, although the mean values for albumin and γ -globulins were significantly below those usually observed in normal subjects or in (M.S.) patients, and the (C.S.F.) findings fell into the normal range. This group of patients was included in this work in order to study the influence of the nutritional status on the protein profile.

No theories are offered to explain the changes of the protein profile in neurological disorders. However, it appears certain that the demyelinating progress per se does not determine these changes, since such conditions as Schilder's disease and posterolateral degeneration with pernicious anemia display a normal protein profile.

(Authors' Abstr.)

Lysergic Acid Diethylamide in Patients with Excess Serotonin

The effects of lysergic acid diethylamide (LSD) were studied in two patients whose blood serotonin levels were elevated as the result of malignant carcinoid. The psychological changes produced by (LSD) in these patients are of the order which have been observed in normal subjects receiving (LSD). It is concluded that elevation of blood serotonin levels does not alter the central effects of (LSD).

(Authors' Abstr.)

Comparison of Chlorpromazine and Reserpine in Treatment of Schizophrenia

In a comparison of the data reported in the literature and in a comparative study of 200 chronic schizophrenic women patients treated with chlorpromazine and 200 chronic schizophrenic women patients treated with reserpine in the same hospital setting by the same personnel, there appeared to be a better clinical response with chlorpromazine.

(Author's Abstr.)

Parkinsonian Reactions Following Chlorpromazine and Reserpine

Four cases are reported in which a Parkinsonian syndrome developed during chlorpromazine administration and also under reserpine medication, each drug given singly. The hypothesis is offered that one or more identical areas in the central nervous system are affected by direct or referred action of either drug.

(Authors' Abstr.)

Scalp and Basal Electroencephalogram During the Effect of Reserpine

An electroencephalographic investigation was made in eight patients under reserpine therapy using scalp and basal leads (two nasopharyngeal and two tympanic electrodes). One of the cases was a normal subject, and two had manic-depressive psychoses with normal electroencephalograms. The remaining five patients were selected according to a definite abnormal brain wave pattern. Two had petit mal; one, grand mal; one had psychomotor seizures, and one was a "rhinencephalic psychosomatic" case.

Under reserpine the basal electroencephalogram showed slow waves of 2.5 c.p.s. and slow theta rhythm in some patients, whereas the scalp electroencephalogram did not show any striking change. In some epilepsy was aggravated with reserpine but improved on anti-convulsants in reduced doses. In the psychosomatic case reserpine behaved as a drug stimulating "dream phantasies".

Some neurophysiological considerations are made on the probable action of reserpine, assuming that it may produce its effect through the Papez neurophysiological circuits.

From this small series the authors are not able to make any definite conclusion. Nevertheless, they can say preliminarily that reserpine seems to produce slow waves and slow theta rhythm in the basal electroencephalogram, with the technique and the doses they used.

(Authors' Abstr.)

Anxiety and Cerebral Excitability

Latency from shock to onset of tonic seizure in patients undergoing E.S.T. is introduced as a simple measure of cerebral excitability when shock is maintained constant.

Seizure latency is highly correlated with level of clinical anxiety immediately preceding E.S.T., greater anxiety giving longer latency. The effect is predominantly determined by change in threshold.

Older patients show significantly longer latency.

Latency tends to increase progressively with continued E.S.T. treatments.

Latency is longer in women than in men, the difference apparently depending on some factor other than threshold.

Depressive and schizoid daily ratings show negligible relation to latency. However, depressed patients as a group show longer latency than schizoaffective patients.

Room temperature and humidity within ordinary limits show poor correlation with latency.

Although latency is primarily affected by anxiety level, the latter shows no consistent progressive change with E.S.T.

The day-to-day "spontaneous" fluctuations in latency and threshold due to level of anxiety correspond to approximately a 20 per cent. variation in stimulus energy.

Correlation is negligible between psychiatric ratings of anxiety, depression, and schizoaffective dissociation.

Both schizoaffective and depressed patients obtain maximum immediate benefit in the first five E.S.T. treatments.

Subsequent treatments produce increasing schizoid dissociation both in schizoaffective and in depressed patients, but particularly in the former.

The cerebral inhibitory function of anxiety and its possible neural mechanisms are discussed.

A theory of initiation of seizures involving an initial inhibitory latent phase is presented.

Parallel animal experiments demonstrate that stress increases latency.

The simplicity and value of a noninterfering latency measurement and psychiatric interview procedure for regulating E.S.T. therapy is emphasized.

(Authors' Abstr.)

Experimental Subcortical Epilepsy

A total of 82 subcortical injections of procaine penicillin G in oil (0.03 c.c.—10,000 units) were made in 25 monkeys. These injections produced 35 spontaneous seizures—an additional 2 were induced with pentylenetetrazol (Metrazol). Electroencephalographic abnormalities followed the injection in 56 animals.

The seizures produced consisted mainly of contralateral focal motor attacks, adverse seizures, and psychomotor attacks.

The EEG concomitants of these attacks consisted principally of an intermittent or continuous focal spiking discharge over the central and, less frequently, the temporal cortex. There were, however, a variety of abnormalities, ranging from localized high-voltage sharp waves to generalized slow-frequency waves.

The lesions were located in most of the basal ganglia, and little specificity for particular seizure patterns for any given structure was noted.

The clinical attacks and EEG abnormalities were largely indistinguishable from those commonly attributed to seizures of cortical origin.

(Authors' Abstr.)

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<i>The Grantham Lobotomy for the Relief of Neurotic Suffering</i>		
Thirty chronic neurotic and psychotic patients in whom neurotic suffering was paramount have been treated by the Grantham lobotomy. Pre-operatively, these patients had been		

refractory to the usual methods of psychiatric treatment. The Grantham operation produced marked improvement in 18 patients, moderate improvement in six, and slight improvement in two. Four were unimproved.

This paper covers the selection of patients, the post-operative course, and the advantages of this psychosurgical procedure. It indicates that the Grantham lobotomy is a tremendous step forward in the treatment of neurotic suffering.

(Author's Abstr.)

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Peganone, a New Antiepileptic Drug

1. Peganone is an effective drug in the control of epileptic seizures.
2. It is most effective against grand mal. In combination with other anticonvulsants it is useful in the control of psychomotor attacks and is of considerable benefit in the difficult variants.
3. The effective daily dose of Peganone is 2 to 3 grams for adults. In children, 0.5 to 1 gram is used.
4. A notable feature of Peganone is the low incidence of side effect, less than any anti-convulsant in the authors' experience. No serious toxicity has been seen. Of particular interest, since Peganone is a hydantoin, is the absence of gum hyperplasia and ataxia.
5. Peganone combines well with other antiepileptic drugs and such combinations often result in control of seizures with no additional side effects. However, if combined with Phenurone it must be used with caution.
6. Because of its effectiveness, synergism with other anticonvulsants, and exceptionally low incidence of side effects, Peganone is, in the authors' experience, a valuable addition to the antiepileptic armamentarium and further clinical evaluation is warranted.

(Authors' Abstr.)

Relation of Chlorpromazine to Epilepsy

1. A brief survey of literature is presented regarding the toxic, epileptogenic properties of chlorpromazine and its effectiveness in the treatment of epileptic disorders.
2. In a group of hospitalized, disturbed epileptic patients a significant improvement in behavior was achieved with the use of chlorpromazine.
3. Occasionally a transient increase in seizure activity occurred under chlorpromazine treatment.
4. Chlorpromazine appears to potentiate the effect of anticonvulsant drugs. This potentiating effect is seldom immediate; there is a critical stage with danger of seizures during the change in medication. The advisable procedure is to continue the previous medication for a while after chlorpromazine is added. If patient remains free of seizures, the dosage of anticonvulsants may be reduced.
5. Although in itself not anticonvulsant and occasionally seizure precipitating, chlorpromazine is valuable in the treatment of epilepsy, particularly if the condition is accompanied by a severe disorder of behavior.

(Authors' Abstr.)

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The Effect of Lysergic Acid Diethylamide on Betta splendens. I

The action of 60 pharmacologic agents has been examined on 22 species of fresh water fish. LSD-25 has a special action on *Betta splendens* which is not found in the other species. This action is partly shared by LAE-32 but not by serotonin, bufotenine, mescaline or adrenochrome. It is potentiated by hyoscine and counteracted by pilocarpine.

(Author's Abstr.)

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Electrophysiological Studies of Hippocampal Connections and Excitability

1. An electrophysiological study of the afferent and efferent pathways of the hippocampus has been made.
2. The excitability of the hippocampus has been studied before and after isolation from the rest of the brain.
3. Evidence for afferent projections to the hippocampus through the fornix has been adduced.
4. Evidence that the dentate gyrus may present an intermediary relay station is advanced.
5. Evidence is presented for connections between the hippocampus and various cortical and subcortical areas, including limbic cortex, amygdala, diencephalic areas and the mid-brain tegmentum.
6. The physiological role of the hippocampus and its significance in seizure discharge are discussed.

(Authors' Abstr.)

Electroencephalographic Rhythms from the Depths of the Parietal, Occipital and Temporal Lobes in Man

Further studies have been done in an effort to establish additional patterns of the electric activity in the depths of the human brain. It has been demonstrated that somatic, sensory, motor, auditory and visual activity can be recorded from the depths of the brain.

Synchronous activity recorded from the ventromedial part of the frontal lobe, parts of the temporal lobe, parts of the parietal lobe and the region of the hypothalamus indicates connections between these regions.

Profound changes in the electric activity in these regions during acute episodes of agitation and hallucination have been observed.

(Authors' Abstr.)

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Effect of Unilateral Brain Injury in Man on Learning of a Tactual Discrimination

This study was concerned with the effect of unilateral brain injury on learning of a tactile pattern discrimination. The experimental group consisted of 36 Ss with unilateral, penetrating brain injury; the control group consisted of 19 Ss with leg injuries.

In the control group, significant and equal amounts of improvement occurred with each hand. In the brain-injured group, the hand on the same side as the injury showed significant improvement, comparable to that of the control group. The hand opposite the lesion, however, did not show significant improvement. This lack of improvement was not related to sensory defect, nor was it related to the lobe injured.

Thus, an impairment in learning appeared after unilateral brain injury, but this impairment was confined to the side opposite the lesion. These data emphasize the importance, for some learning, of that hemisphere which receives the main projections from the stimulated surface.

(Authors' Abstr.)

A Further Study on the Retroactive Effect of ECS

Five groups of rats were given training on a horizontal-vertical discrimination problem. For four groups, one electroconvulsive shock was administered at 10 sec., 2 min., 1 hour, and 4 hour, respectively, after reaching the criterion of mastery. The fifth group constituted the normal controls. Two days later, all groups were required to relearn the discrimination.

The results of this study showed the following:

1. The groups receiving a shock at 10 sec., 2 min., and 1 hour after mastering the discriminative response showed significant deficits in memory of the habit, the deficit being inversely related to the time interval.

2. There was no significant difference in retention of the habit between the control Ss and those Ss receiving a shock 4 hour after learning the problem. These results were discussed in terms of a perseveration theory of memory.

(Authors' Abstr.)

Analysis of the Effects of Frontal Lesions in Monkey. I. Variations of Delayed Alternation

Four operated with lesions of lateral frontal granular cortex and four operated controls were trained on a series of delayed alternation problems presented in the following order: "left-right" alternation, "up-down" alternation, and "go-no-go" alternation. The control operated required an increasing number of trials to learn the consecutive problems, but all attained criterion on all three tasks. The anterolateral frontal operated, in contrast, failed, within the limits of training, to achieve 90 per cent. correct performance on any of the tasks, although their final scores on "go-no-go" alternation fell just short of this criterion. The relatively successful performance of the anterolateral frontal operated on the "go-no-go" procedure cannot be explained entirely as an effect of general delayed-alternation training since comparable improvement did not appear on the classical problem when this task was given subsequently. The results suggest that while difficulty specific to the "left-right" response choice cannot account for frontal operated's severe impairment on traditional delayed-response-type tasks, some factor other than, or in addition to, the delay would appear to be of critical importance.

(Authors' Abstr.)

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Analysis of the Effects of Frontal Lesions in Monkey. II. Variations of Delayed Response

The performance of four frontal and four temporal control operates was compared on a series of eight delayed-response tasks. These tasks included traditional delayed response and three variations, each presented by both the direct and indirect methods of baiting. The variations of delayed response employed (a) nonpositional instead of positional predelay cues; (b) a "go-no-go" instead of a left-right response choice; and (c) both cue and response variations combined. The results demonstrated that frontal operates perform nearly as well as control animals whenever traditional predelay cues are replaced by nonpositional cues, irrespective of the response choice, or whether direct or indirect baiting is employed. These findings suggest that frontal operates' impairment on traditional delayed-response-type problems is related, not only to the delay, but to some aspect of the predelay cue as well.

(Authors' Abstr.)

Analysis of the Effects of Frontal Lesions in Monkey. III. Object Alternation

Four frontal operates were trained approximately one year after surgery on an object alternation task, and their performance compared with (a) their own performance on classical spatial alternation and (b) the performance of four temporal operates on the object alternation. Results demonstrated that frontal lesions interfere equally with performance on both forms of alternation. This conclusion as confirmed in a second experiment that investigated retention on the two tasks following anterofrontal and inferotemporal lesions. On the basis of the results of the current experiment, the successful performance of frontal operates on delayed-response-type problems observed in earlier experiments was accounted for in terms of the "distinctiveness" which the predelay cues had acquired from contiguity with distinctive responses and differential reward.

(Authors' Abstr.)

Immediate and Chronic Disturbances on the Delayed Response Following Transection of Frontal Granular Cortex in the Monkey

Four rhesus monkeys were trained on the delayed response prior to surgery. They were tested within a few hours following a trephining procedure and for several days thereafter, within a few hours following frontal lobotomy and for 14 days thereafter, and just before sacrificing several weeks later. The data indicate that

1. Effects of lobotomy appeared within 1½ to 6 hours following surgery. No delayed effects were detected.
2. Primary effects persisted for at least 10 weeks.
3. Transient effects, possibly not the direct result of the primary lesion, disappeared by the 5th to the 13th day.

These results are discussed in relation to the logic of the ablation method.

(Author's Abstr.)

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The Cerebral Electrographic Changes Induced by LSD and Mescaline are Corrected by Frenquel

1. A cerebral electrographic change, consisting in a long lasting alerting effect, follows the injection into rabbits of (LSD) in small amount (1-15 gamma/kg.) and of mescaline. These findings correlate with (EEG) observations in psychotic patients and in volunteers under the action of (LSD) and mescaline.

2. Frenquel, which corrects the (LSD)-induced experimental psychoses, also eliminates the electrographic changes evoked by (LSD) and mescaline.

3. (LSD) in large amounts (20-60 gamma/kg.) has an effect on the cerebral electrical activity opposite to the one produced by small doses (1-15 gamma/kg.). This is correlated with the observation that (LSD) in very large quantities has a tranquilizing action.

4. These observations are tentatively explained on the basis of their pharmacological data and those of others. The production of electrographic alertness by the hallucinogenic drugs and their psychotogenic effect are attributed to a serotonin-facilitating property. The correction of the electrographic (LSD) or mescaline-induced abnormalities by the use of Frenquel is attributed to the serotonin inhibiting properties of that drug.

(Authors' Abstr.)

Rhencephalic Activity During Thought

Patients with chronically implanted cortical and subcortical electrodes provided an opportunity for an exploratory study of the electrical activity of these areas during interview. These studies demonstrate distinct, reproducible changes in electrical recordings localized to the amygdaloid and rostral hippocampal regions. These changes were correlated with both thought activity elicited during directed interviews and occurring spontaneously. It was suggested that this type of rhencephalic activity is related to emotionally significant memories. Similar electrical responses were elicited by olfactory stimuli and thoughts related to odors.

(Authors' Abstr.)

Chemical Constituents of Human Brain

Areas from the brains of fetuses and babies dying in the neonatorum as well as from adult brains have been analyzed for water, cholinesterase, total nitrogen and free L-glutamic acid.

Cholinesterase activity is highest in the caudate both in the young and in the adult. In cortex, thalamus and superior colliculi, this enzyme appears to decrease with age.

In the immature brains, the distribution of total nitrogen and of free L-glutamic acid follows a neurophyletic pattern. In the adult brains this pattern is apparent only for water. Both nitrogen and L-glutamic acid increase in the adult brains on a fresh tissue basis.

Analyses of samples taken from different areas of the cortex suggest that each area has a unique chemical composition.

The relation of these findings to data available for other species is discussed.
(Authors' Abstr.)

Clinical, Psychological and Myoneural Changes in Psychotic Patients Under Oral Serpasil Medication

1. Eighteen out of 22 severely disturbed chronic schizophrenics from the maximum security ward of a state hospital showed improvement under oral Serpasil treatment; half of them, marked improvement.

2. Clinical rating, psychometric, projective and expressive psychological tests basically agree on the effectiveness of the drug.

3. The authors feel that present psychological tests are not adequate for the quantitative evaluation of changes in severely psychotic patients.

4. Due to cautious increase of individual doses and adherence to oral medication, side reactions were minimal.

(Authors' Abstr.)

Studies on Mescaline. VI. Therapeutic Aspects of the Mescaline-Chlorpromazine Combination

1. The use of mescaline and chlorpromazine as a therapeutic technique has been described.

2. Eighteen of 40 acutely ill patients showed a complete remission of symptoms, and seven showed a partial improvement. Only seven of 17 chronically ill patients showed any improvement at all.

3. The therapeutic action was most marked in those patients who had been ill a short period of time before admission and were rapidly treated after admission.

4. Mescaline-chlorpromazine is most valuable as a therapeutic technique when used in a psychodynamic frame of reference.

(Authors' Abstr.)

Pharmacotherapy in Children With Psychiatric Illness

1. One hundred and ninety-five children on a psychiatric ward have been treated with a series of six drugs: Benadryl, Tolserol, Artane, Ambodryl, Thorazine and Serpasil. A methodology is described for the study of such compounds that includes the use of placebo.

2. The Benadryl appears to have the best over-all effect and was particularly helpful in those children with primary behavior disorders displaying anxiety.

3. Thorazine was most beneficial for hyperkinetic, agitated, schizophrenic children.

4. Tolserol produced improvement in children with the diagnosis of organic brain disorder.

5. The results with Artane, Ambodryl and Serpasil did not appear to be significantly different from those obtained with placebo.

6. The drugs did not appear to alter the basic psychopathology found in the children.

7. Pharmacological agents have an indisputable role in the management of children in a psychiatric hospital setting.

8. Necessity for further research in this area is indicated.

(Authors' Abstr.)

Studies in Human Cerebral Function: The Effects of Mescaline and Lysergic Acid on Cerebral Processes Pertinent to Creative Activity

The action of mescaline and lysergic acid was that of inhibition or depression of the usual regulated activities of the subjects. The four graphic artists who ingested these drugs had impairment of their highest integrative functions as described above.

They, nevertheless, created works of greater esthetic value appeal according to the panel of fellow artists, but this was associated with a relaxation of control in the execution of lines and employment of color, so that both color and line were freer and bolder. The effects on sensory function were such as to augment the perception of dull areas in their paintings, but detached the colors from their relationship to the whole esthetic structure. Furthermore, the benefits derived from these agents were offset by the difficulty these subjects had in mobilizing their perceptions and energies in the pursuit of creative art.

(Authors' Abstr.)

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A Comparative Study of the Effect on Anxiety of Chlorpromazine, Reserpine, Phenobarbital, and a Placebo

This investigation was undertaken to evaluate the relative effectiveness of Chlorpromazine, Reserpine, Phenobarbital and a placebo on symptomatic manifestations of anxiety. A total of 84 voluntary psychiatric admissions in a V.A. General Hospital completed a 30-day course of one of these four preparations. Subjective, psychiatric, physiological and psychological measures were employed to evaluate changes before and after treatment. The findings of this investigation revealed:

1. Patients in each of the four groups reported a significant reduction in the number of manifest symptoms of anxiety after the 30-day treatment. When the drugs were compared with each other, no significant differences were found.

2. On an anxiety rating scale completed by each patient before and after treatment, significant differences in diminution of over-all anxiety were achieved in all the groups, except placebo. No significant differences were found when the groups were compared with each other.

3. When the patients were evaluated psychiatrically before and after treatment, significant improvement was evidenced in all groups except patients on Phenobarbital. When Chlorpromazine was compared with Phenobarbital, a significant difference was found in favor of Chlorpromazine. All other group comparisons yielded negative results.

4. The critical flicker fusion test was employed to evaluate levels of anxiety. Patients in the Reserpine group alone demonstrated significant changes in the critical flicker fusion score upon completion of treatment. It is to be noted that the Reserpine lower post-treatment CFF score was in the opposite direction to that hypothesized in previous research studies. These findings would suggest the desirability of further study. Several possibilities emerged from this investigation. While it has been formulated that "the anxious person being preoccupied with the internal state of affairs directs less attention to the external reality, flicker" (3), it may very well be that with certain levels of anxiety, the anxious person has need to hold on to reality longer. There may also be a physiological factor in Reserpine and possibly Chlorpromazine which independently effects the visual response to the CFF (12).

5. The association of weight gain and reduction in anxiety is a common clinical observation. Significant weight gains were recorded only with patients in the Reserpine group. These patients differed significantly from patients on Phenobarbital and Chlorpromazine with respect to weight changes.

6. Reserpine patients were the only group to demonstrate significant reductions in systolic and diastolic blood pressure. On Chlorpromazine, a significant reduction was noted only in systolic blood pressure. However, in neither case did the lowered blood pressure produce any untoward side effect.

7. When Reserpine and placebo patients were compared, significant differences were found in weight, systolic and diastolic blood pressure, and on the critical flicker fusion test. A significant weight difference favoring Reserpine was indicated when Reserpine and Chlorpromazine were compared. A significant difference in favor of Reserpine was similarly found on the CFF test when this drug was compared with Phenobarbital.

One patient on Chlorpromazine developed hepatitis, and one patient on Phenobarbital became dizzy and hypotensive. No other untoward effect accompanied the utilization of any of the drugs (10).

In evaluating the results of this study, consideration should be given to the limiting effects of the influence of hospitalization, the nature of the psychiatric patient population, the duration of the course of treatment and the dosages employed. The over-all results of this study indicate that each drug was efficacious in reducing symptomatic manifestations of anxiety. While isolated instances pointed to the superiority of Reserpine and Chlorpromazine, few significant differences were observed when the drugs were compared with each other. Previous research and clinical experience at this and other hospitals suggest that Chlorpromazine and Reserpine are far more effective with marked agitation and panic states than with the alleviation of the kind of overt manifestations of anxiety studied in this investigation.

(Authors' Abstr.)

Controlled Study on Clinical Use of Reserpine in Psychotic Patients with Special Comments on Sources of Error

A controlled study was conducted on 195 patients, 151 of whom were on reserpine and 44 of whom were on a placebo for 4½ months. Of the patients on reserpine 23·2 per cent. showed marked improvement, 37 per cent. showed moderate improvement, and 27·2 per cent. showed slight improvement. Of the 44 controls on placebo only 4·5 per cent. showed improvement, and 29·5 per cent. showed slight improvement.

Observations concerning possible errors in a clinical study of this nature are described.

Hence the need for further verification of the clinical value of reserpine in mental disease is required.

If ultimately proved to be effective, even in a moderate percentage of cases, its potential therapeutic value is immense.

The use of such a drug to further investigate mental mechanisms may also be significant.
(Author's Abstr.)

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The Effects of Reserpine (Serpasil) on the Chronic Disturbed Schizophrenic: A Comparative Study of Rauwolfia Alkaloids and Electroconvulsive Therapy

The effect of Serpasil was studied in 80 severely ill long-stay schizophrenic patients to determine whether its use would prove superior to, equal to, or inferior to electroconvulsive therapy as a maintenance measure.

These patients formed a homogeneous group of "difficult management problems", requiring excessive medical and nursing care, restraints, heavy sedation, seclusion, hydrotherapeutic and pack treatments. They were divided into four matched groups of 20 each, receiving: A, placebo; B, Serpasil; C, placebo and electroshock; and D, Serpasil and electroshock. To avoid prejudice in the evaluation of improvement, no one except the author knew the design of the experiment.

Two standards for measuring improvement were employed: first, amenability to nursing procedures and the change in the patient as a ward citizen; secondly, clinical improvement, based on psychiatric interviews. The senior nurse and her assistant evaluated the amenability of the patient weekly. The author and a physician with long knowledge of the cases but with no knowledge of their experimental grouping determined the clinical scores weekly for the first eight weeks and then fortnightly. The scores were expressed numerically and plotted graphically in addition to the full recording of medical opinion.

The results showed that Serpasil produced beneficial effects which were superior to maintenance shock treatment in the severely ill long-stay schizophrenics. Twenty-five per cent. of these cases were markedly improved; 50 per cent. were moderately or mildly improved. The remaining 25 per cent., although psychiatrically unimproved, were easier to manage from a nursing standpoint.

These results and techniques of administration of Serpasil are discussed. Best results were achieved by starting with 2.5 mg. parenterally twice daily for the first week and transferring the patient to 5.0 mg. orally twice daily during the second week. Thereafter, the most satisfactory regimen was one that employed individualization of dosage. It is emphasized that favorable results were obtained in cases which had not previously yielded to one or more known methods of treatment.

(Author's Abstr.)

The Use of Metrazol as a Mood Conditioning Drug: A Discussion as to Its Mode of Action

The role of Metrazol as a mood conditioning drug has been carefully evaluated. It is our clinical impression that in arteriosclerotic patients Metrazol does tend to modify social behavior. Psychometrically, measurable improvement is noted in orientation, in ability to size and comprehend a practical social situation and in associate learning of new and unfamiliar material. However, the same testing shows Metrazol to have a detrimental effect on visual reproduction requiring a high level of integration of visuomotor functioning, and also on the mental control needed for prolonged attention and concentration.

Although the clinical impression of improvement was not as clearly borne out by the psychometric studies, it was felt that a broader spectrum of tests and/or a greater number of subjects might resolve this ambiguity.

The site and mode of Metrazol's action are discussed. This included a reference to the possible relationship between it and the degradation products of epinephrin.

The psychological changes which follow the use of mood conditioning drugs indicate that care should be exercised in their selection. Some of the factors, which may govern the use of tranquilizing as opposed to analeptic therapy, have been presented.

(Authors' Abstr.)

An Attempt to Demonstrate a Catatonigenic Agent in Cerebrospinal Fluid of Catatonic Schizophrenic Patients

An experiment was designed to test the hypothesis that there is a catatonigenic agent in the cerebrospinal fluid of catatonic patients.

Concentrated cerebrospinal fluid from catatonic and mental defective patients, as well as an isotonic saline and an artificially-reconstituted cerebrospinal fluid solution, was injected subcutaneously into young rats. Performance of these rats in a rat-activity wheel was recorded for 24 hours prior to and after the injections.

Although the cerebrospinal fluid from the mental defectives depressed the activity of the rats more than the cerebrospinal fluid from the catatonics in the first 10 to 15 hours and the catatonic fluid depressed the activity of the rats more than the mental defective fluid in the later hours, these differences were not statistically significant. There was a significant difference between the activity of the rats injected with isotonic saline, artificial cerebrospinal fluid and the human fluid in the early hours. Some time after 10 to 15 hours there was no significant difference between any of the groups. The performance of the rats in the activity wheel was related to the hypertonicity of the injected solutions.

The mechanisms determining the different activity curves of the injected animals were discussed, as well as the variables and other difficulties involved in this investigation.

The author's observations did not substantiate the hypothesis that there is a catatonigenic agent in the cerebrospinal fluid of catatonic patients.

(Author's Abstr.)

Kemadrin, a New Drug for Treatment of Parkinsonian Disease

Kemadrin, a new synthetic spasmolytic agent, has been used for periods of three to seven months in combination with other drugs in a series of 30 severe Parkinsonian patients. Twenty-one of these patients showed significant improvement, especially in regard to decreasing rigidity, increasing ability in accomplishment of usual activities, and elevation of mood and alertness. There were very little untoward symptoms with the use of this agent; rather it was possible by decreasing the dosage of the other drugs, in more than half the cases that were improved, to reduce annoying dryness of the mouth, mydriasis, drowsiness, depression and confusion which had complicated the treatment in most of the patients in this series. Twenty of these Parkinsonian sufferers were either of the post-encephalitic type or of unestablished etiology, and 10 could be classified as arteriosclerotic or pre-arteriosclerotic. The choice of patients in this series was based on severity of symptoms and inadequate control of symptoms with the other usual medications employed in the treatment of this illness.

Kemadrin is procyclidine hydrochloride and is closely related to Artane and Patitane. Its therapeutic effects are similar to those of these drugs, but it has considerably less untoward reactions in doses up to 40 to 50 mgm. daily, even without decrease in dosages of the other drugs used in combination. This new drug, Kemadrin, shows promise of definite value in the armamentarium of the physician in the treatment of Parkinsonism, especially in those cases which have not responded favourably to other drugs.

(Author's Abstr.)

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Intralaminar Distribution of Cytochrome Oxidase and DPN in Rat Cerebral Cortex

The quantitative distributions of diphosphopyridine nucleotide and cytochrome oxidase have been determined within the cytoarchitectonic layers of rat somatosensory isocortex.

DPN concentration is greatest in layers IIa, IIIb-IV, and Vc. Cytochrome oxidase activity is rather uniformly distributed through layers I-V but, like DPN, is more active, relative to immediately adjacent zones, in layers IIa, IIIb-IV, and in the middle or lower third of layer V. Its activity becomes progressively less as sampling is carried through layer VI into the subcortical white matter.

The intracortical distribution patterns of these respiratory enzymes presumably reflect the relative rates of biological oxidations at the different architectonic levels and indicate that layers II, III, and IV have the highest rates of energy metabolism. The anatomical significance of the architectonic patterns of DPN and cytochrome oxidase has been discussed, and the conclusion reached that their intracortical distributions are consistent with primary localization in the cytoplasmic particles of the nerve cell bodies and their dendrites.

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Mescaline and LSD-25 in Activation of Temporal Lobe Epilepsy

Mescaline and LSD-25, administered to three patients who had temporal lobe epilepsy, did not provoke psychic auras or any causally related material. The electroencephalographic changes were minimal and were associated with the action of mescaline and LSD-25, rather than as an activation of a focus.

(Authors' Abstr.)

Investigation of the Primate Amygdala: Movements of the Face and Jaws. 2. Effect of Selective Cortical Ablation

The authors have removed the cortical representations for face, lips, jaws, and tongue on both sides in different monkeys. After these cortical removals they obtained movements of face and jaws as they stimulated the amygdala on one or the other side. They have evoked ipsilateral facial movements and some movements of the jaws during stimulation of certain regions of the lateral temporal cortex. This has been the experience of Schneider and Crosby. However, they removed these areas of the lateral temporal cortex. In these animals stimulation of either amygdala was followed by movements of the face and jaws identical to those which they have described in animals whose cortical areas were intact.

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Response of Psychiatric Patients to Massive Doses of Thorazine. I. Behavioral and Clinical Analysis

The following results were obtained:

1. Change in Status Following Thorazine. (a) Objective behavioral ratings: The mean score for the group increased significantly from pre-treatment to mid-treatment to post-treatment ratings. Significant improvement occurred over the entire course of treatment ($P < .001$). (b) Clinical ratings: Significance tests (t-tests, chi-square tests) indicated definite improvement in psychiatric status as measured by the clinical rating scale of change in status. In no case did a patient's behavior deteriorate. (c) Specific behavioral areas improved: The 100 items of the objective behavioral rating scale were submitted to individual item analysis under the hypothesis that change would occur in the direction of greater mental health following thorazine. Twenty-seven items showed significant shift in this direction with

thorazine treatment. Qualitative and quantitative evaluation indicated that this group of items was highly saturated with statements concerning increase in overt activity and in communication and socialization. This was of special interest, since other studies have tended to indicate that thorazine is most useful for calming patients who are excessively excited or overactive.

2. Physiological Cues to the Outcome of Treatment. Several physiological measures were subjected to analysis in an attempt to derive cues early in treatment, which might presage ultimate behavioral and psychiatric improvement. None of the several measures studied were significantly related to improvement. However, a measure of pulse rate variability during the first two days of treatment showed a tendency toward an inverse relationship to ultimate improvement following thorazine ($P=.10$).

3. Relationship Between Improvement and Age or Chronicity. (a) Improvement and age: A comparison of the oldest with the youngest patients gave no reason to reject the null hypothesis that age was unrelated to the results of thorazine treatment as administered by the procedure employed. (b) Improvement and Chronicity: Similarly, significance tests gave no reason to reject the null hypothesis that behavioral improvement over the course of thorazine was unrelated to chronicity of the mental illness.

The over-all findings point to definite psychiatric and behavioral improvement in the patients studied, following a course of massive thorazine treatment.

(Authors' Abstr.)

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