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Brain Copper-Protein Fractions in the Normal and in Wilson's Disease

Brain proteins in hepatolenticular degeneration, like those in normal brain, can be separated into three copper-containing fractions: Fraction I, extracted with 0·1 M acetate buffer pH 4·5 (or with water or with 0·1 M bicarbonate buffer pH 8·2); Fraction II, extracted at pH 3·5 and vanishing ionic strength, and the residual Fraction III.

The greatest absolute amount of pathological brain copper in hepatolenticular degeneration is extracted in Fraction I. Of this Fraction I copper, slightly more than one-half is nondialyzable at pH 4·5 and may or may not be identical with the Fraction I copper of normal brain.

A significant portion of the pathological copper in the brain in hepatolenticular degeneration is present in a form not found in appreciable amounts in normal brain. This abnormal copper-protein combination is similar to normal Fraction I in being soluble both in 0·1 M acetate buffer pH 4·5 and in 0·1 M bicarbonate buffer pH 8·2, but is different from normal Fraction I copper-protein(s) in its failure to retain copper on dialysis at pH 4·5.

The finding that bicarbonate buffer extracts of the fresh tissue do not lose copper on dialysis against bicarbonate buffer indicates that substantially all of the copper in the brain in hepatolenticular degeneration is bound in undialyzable form, presumably to proteins.

(Authors' Abstr.)

Motivational Determinants in Modification of Behavior by Morphine and Pentobarbital

Since the description of drugs as either "stimulant" or "depressant" did not appear to be sufficient to account for their behavioral effects, it was proposed that motivational factors must be considered as partial determinants of such effects. The present experiment, designed to test this hypothesis, was carried out on 182 former narcotic addicts. Visual-manual reaction times were measured on separate groups of subjects after the administration of 15 mg. of morphine sulfate or 250 mg. of pentobarbital sodium, and these were compared with the reaction times of other subjects who received no drug on the test day. Each of these measurements was made under four conditions which differed from each other with respect to the incentive (morphine reward) offered for participation in the experiments.

The results indicate that changing incentives significantly modifies control reaction time, as well as the effects of morphine or pentobarbital thereon. Thus, in comparison with the control, both drugs acted either as "stimulants" (accelerated reaction time) or as "depressants" (slowed reaction time) or had no effect, depending on the particular incentive conditions under which they were administered. The actions of these drugs, however, were "specific" with respect to each other: The effect of pentobarbital changed from "depressant" to "stimulant" when conditions changed from "Low Incentive" to "High Incentive", while the action of morphine changed from "stimulant" to "depressant" when identical changes in incentive level were made. Viewed from another standpoint, the results indicate that sensitivity to changes in incentives is reduced by morphine and enhanced by pentobarbital.

It is postulated that changes in incentive levels, manipulated by the observer, alter performance through effects on specific motivations. Hence, from the data presented, it is inferred that performance, as well as the effects of drugs thereon, is determined in part by the particular motivations that obtain when the measurements are made. The "specificity" of the effects of any particular drug will therefore be apparent only if the motivations involved in the behavior studied are controlled.

Furthermore, it is concluded that drugs exert "specific" effects on particular motivations, and that differences in the attractiveness of drugs for different persons may be partly explained on the basis that motivations acceptable to the subject can be enhanced and unacceptable ones suppressed by use of particular chemical agents.

(Authors' Abstr.)

Some Observations on the Use of Tranquillizing Drugs

The purpose of this essay is to inquire into, and call attention to, some sociopsychological aspects of the current vogue of using tranquilizing drugs in psychiatric disorders.

The use of these drugs rests on the premise that psychiatry deals with "mental illness" and that such illness presents a problem essentially analogous to that encountered in medicine (and particularly in infectious disease). There is evidence to suggest that this "medical" model of behavioral disturbance is inadequate and misleading. If such disturbances do not constitute "diseases" which manifest themselves in certain "signs" and "symptoms", then measures based on this concept are likely to be faulty, and probably harmful to patient, physician, or society.

A brief analysis of this problem is organized around the following three questions: (1) What do we, as physicians and psychiatrists, do when we prescribe tranquillizing drugs? (2) Whom do we treat? (3) Is this form of treatment justifiable? The generally accepted answers to each of these questions are summarized. They are followed by suggestions for additional possible "answers", the most important of which are (1) that the use of these drugs may represent a new "symptom" of the ancient occupational disease of physicians known as "furor therapeuticus"; (2) that we treat ourselves and the patient's social environment; and (3) that whether we hold the treatment to be justifiable or not will depend on what position we take *vis-à-vis* the patient's conflict with other persons and society.

In conclusion, the role and significance of defiance of authority and of deviance from social norms in "mental illness" (and in all modes of human life, for that matter) are briefly mentioned. These considerations are emphasized in an effort to substantiate the legitimacy, and possible value, of taking a position of caution and criticism with respect to the widespread use of tranquillizing drugs in medical and psychiatric practice.

(Author's Abstr.)

Frontal Lobe Damage and Flicker Fusion Frequency

Matched groups of patients who had sustained bilateral prefrontal lobotomy, hospitalized control patients (non-surgical), and normal control subjects were tested for flicker fusion frequency. Surgery for the operatee group had been performed from eight to nine years prior to testing. Pertinent control criteria were race, age, sex, period to time institutionalized, amount of schooling, and pre-operative diagnosis. The findings of the study are as follows:

1. The frontal lobe damage sustained in prefrontal lobotomy is not reflected in a permanently depressed fusion point.
2. There is no indication that lobotomized subjects are objectively more accurate (less variable) in locating their fusion point than are hospitalized control or normal control subjects.
3. A definite linear decrease in fusion frequency level with age is found in patient and in normal subjects.
4. The most pronounced drop in fusion level with age occurs between 45 and 55 years of age.
5. The extent to which a subject varies or deviates from his own fusion point in successive trials does not appear to be dependent on age. There is nothing to indicate that older persons are less variable than young persons.

(Author's Abstr.)

FEBRUARY

Mental Function and Cerebral Oxygen Consumption in Organic Dementia

Clinical, neurophysiological, and psychological data were obtained and evaluated individually for 19 subjects. Clinically, 6 were normal; 3 had questionable dementia; and 10, indisputable dementia.

The cerebral metabolic rate of oxygen ($CMRO_2$) was measured in cubic centimeters of O_2 per 100 gm. of brain per minute by the Kr^{85} method, using bilateral sampling of internal jugular venous blood. The clinically normal group had a $CMRO_2$ of 3·6–3·2; the intermediate group, a $CMRO_2$ of 3·2–3·0 and the demented group, a $CMRO_2$ of 2·8–1·6.

Arguments are advanced that abnormally low $CMRO_2$ (3·0 or below) in patients without acute cerebral affections indicates cortical atrophy—a conclusion confirmed by air encephalography for the five subjects so examined.

The psychological grouping of the patients was based on the presence or absence of fluctuations during learning and on two criteria derived from a block-pattern test. The four groups thus obtained comprised one without abnormalities, and three of increasing mental dysfunction. These groups correlated well with the $CMRO_2$ values in all cases.

Observations for the six patients with $CMRO_2$ values of 3·0 to 2·6 suggest that the psychological method described offers possibilities for the diagnosis of slight organic dementia.

(Authors' Abstr.)

Flicker Fusion Thresholds in Multiple Sclerosis

The central visual flicker-fusion thresholds of 20 male veteran patients with multiple sclerosis and 20 control subjects with no central nervous system disorder, are compared. A markedly impaired flicker discrimination is found in the M.S. group. Only three M.S. patients had evidence of scotomata; however, nine possessed some degree of optic pallor. The pallor group manifests the greatest impairment of flicker discrimination, but the non-pallor M.S. group shows also significantly lower values than the controls. It is suggested that these results are due mainly to optic neuropathy accompanying retrobulbar neuritis. These effects apparently are not revealed by standard visual field examinations but do appear when flicker-fusion thresholds are determined.

(Authors' Abstr.)

Common Medical Disorders Rarely Found in Psychotic Patients

Hay fever, asthmatic attacks, and the acute stages of rheumatoid arthritis are extremely rare among psychotic patients.

Duodenal ulcer is not rare in psychotics and is probably just as frequent as in the general population.

An attempt is made to apply existing physiological and psychological hypotheses in the explanation of these facts.

(Author's Abstr.)

Studies in the Effects of Lysergic Acid Diethylamide (LSD-25)

This study is concerned with the effect on spatial localization of lysergic acid diethylamide (LSD), assumed to be a primitivizing drug. Normals and schizophrenics, with and without LSD, adjusted a luminescent rod in a darkroom to apparent verticality under various conditions of body tilt and different initial setting of the rod (starting position).

With LSD, for normals and schizophrenics, the apparent vertical is displaced in the direction opposite to the side of body tilt. Under LSD this displacement is significantly increased for normals; for schizophrenics there is no evidence that the drug significantly alters the effect of body tilt on perception of verticality.

Without LSD, for schizophrenics and normals, the effect of starting position is that of displacement of the apparent vertical from the plumb line in a direction toward the position in which the rod is placed at the beginning of the trial. For normals as well as for schizophrenics LSD increases the starting position effect; this increase is not significant in normals but highly significant in schizophrenics.

The differential effects of LSD are evaluated with reference to the assumption that LSD operates as a primitivizing agent.

Additional comparisons between normals and schizophrenics with respect to the effect of body tilt and starting position on apparent verticality without LSD are included.

(Authors' Abstr.)

Diagnostic Testing for Cortical Brain Impairment

By using both the Spiral After-effect Test and the Graham Kendall Test, the diagnosis of cortical brain impairment is greatly facilitated. Cases missed by one are detected by the other test. The two supplement each other and together make a highly valid battery for determination of cortical involvement.

(Authors' Abstr.)

MARCH

The "March" of Temporal Lobe Epilepsy

The convulsive attacks of 40 patients with psychosensory or psychomotor epilepsy have been subjected to sequential content analysis. Certain patterns of seizure organization appear from such analysis, suggesting an ordered "march" of seizure manifestations in convulsive attacks originating in the temporal lobes and environs.

The varied subjective manifestations of individual attacks indicate strong relationship of epigastric sensation, subjective fear, and motor behavior of the flight-fight pattern. On the contrary, the small group of patients with cephalic aura experience relatively pleasant anticipatory states, free of fear components. Vertigo and tinnitus are followed by illusory states in three-fourths of the patients studied, and fear was present in only one of the seven patients in this group. The disagreeable odor characteristic of the "uncinate fit" never appeared as a first symptom of attack in the eight patients reporting this sensation, and most commonly succeeded the subjective state of fear. Olfactory aura of pleasant nature, much rarer, was always a first symptom of an attack, and was not followed by fear-flight-fight manifestations but always was succeeded by a sense of intense mental confusion.

Preliminary analysis of the content and sequence of this group of psychosensory and psychomotor attacks appears to offer a doorway into greater understanding of the organization of emotional feeling and expression.

(Author's Abstr.)

Asynchronism of Electrical Activity of Frontal Lobes During Sleep

Electroencephalographic studies on 202 patients with frontal lobotomy indicate that the only consistent electroencephalographic finding resulting from this operation is an asynchronism of slow activity in the frontal areas during deep sleep. This abnormality never appears before the 18th post-operative month. It becomes increasingly common and evident thereafter and is found in all cases 36 months or more after operation. This change is permanent and irreversible. The abnormality is restricted to the frontal lobes, and only the slow activity of deep sleep in the frontal lobes is affected. Sleep spindles and all other patterns in the frontal areas and elsewhere remain normal; in other areas the slow activity of deep sleep is undisturbed.

It is assumed that this late-appearing asynchronism of slow activity in the frontal areas during deep sleep results from a delayed degeneration of commissural fibers which link certain nuclei in the left and right thalamus.

(Authors' Abstr.)

Chlorpromazine (Thorazine) Treatment of Disturbed Epileptic Patients

The majority of emotionally disturbed epileptics show an excellent response to chlorpromazine.

Anticonvulsant medication must never be reduced while the patient is on chlorpromazine therapy.

Potentiation or intensification of barbiturate effect is apparently of little or no clinical significance.

Anticonvulsant drugs should be increased or supplemented at the earliest indication of any seizure increase during chlorpromazine therapy.

Chlorpromazine is well tolerated, without any marked alteration in the seizure frequency in most epileptics.

Maintenance dosage is established by trial and error and may be necessary for prolonged periods.

(Author's Abstr.)

The Pattern of Conduction of Amygdaloid Seizure Discharge

The conduction of electrical after-discharge induced by electrical stimulation of the amygdaloid nucleus was studied in 19 cats in order to understand the functional anatomy of seizure mechanisms in ictal temporal lobe automatism in man known to be dependent upon epileptic discharge originating in the amygdaloid region. The findings are as follows:

1. The subcortical structures fired by amygdaloid after-discharges extend from the septal area back to the mesencephalon, with inclusion of the whole diencephalon, hypothalamus, and thalamus as well.

2. There is a rather sharp contrast between the diffuse and extensive subcortical conduction of amygdaloid seizure discharge and the restricted conduction to cortical regions.

3. The cortical areas fired by amygdaloid after-discharges comprise the hippocampus and those cortical areas of the cat's brain that are homologous to man's anterior temporal and insular cortex. These findings in the cat are in agreement with the topographical distribution of epileptic discharges in patients with ictal automatism due to discharge in the amygdaloid region.

4. Amygdaloid after-discharges are preferentially conducted to subcortical structures. Among these subcortical structures, the most constant firing occurs in the basal diencephalic and mesencephalic tegmental areas, the same regions which, on the basis of previous experiments, are known to represent the direct subcortical projection fields of the amygdala.

The mechanism of propagation of amygdaloid after-discharges to the thalamus may be related to the marked build-up of an excitatory state occurring in response to repetitive amygdaloid firing, which in cases of intense amygdaloid discharge, as in seizure activity, may supposedly become vigorous enough to allow propagation of discharge from the basal diencephalon and the brain stem into the thalamic gray matter.

The conduction to the ipsilateral "temporoinsular" cortex is more labile than that to the thalamus, and even more labile seems to be that to the contralateral amygdala and the contralateral temporoinsular cortex.

The preferential conduction of amygdaloid after-discharge into highly integrative formations of the subcortex tends to corroborate Penfield's hypothesis that the phenomena of ictal epileptic automatism may be explained on the basis that seizure discharge originating in the amygdala actively fires into the "centrencephalic system".

The frequent electrographic suppressor onset of temporal lobe seizures originating in the amygdaloid region was re-duplicated in some of these animal experiments. Its possible relationship with the generalized cortical low-voltage activity, as often produced by amygdaloid stimulation, is discussed.

(Author's Abstr.)

Sites of Origin of Hypoglycemic Seizures in the Rabbit

An electroencephalographic study has been made of the characteristics, sites of origin, and projection of hypoglycemic seizures in the restrained, non-curarized rabbit. Records were made of the electrical activity of the cerebral cortex and subcortical centers approached by stereotaxic means. The results reveal that insulin-induced hypoglycemic seizures arise in and may be confined to the amygdala and/or the hippocampus. Severer seizures may project to the pre-optic, hypothalamic, and other brain stem regions without reaching the frontal or limbic cortical area. The localized seizures are not accompanied by any apparent somatic motor activity and are detected only by the deep electrodes. Increased secretion of adrenaline following surgery and stereotaxic restraint may counteract the effect of quite massive doses of insulin to the extent that the blood-sugar level is not lowered to the seizure range. The adrenal effect may be counteracted by cutting the splanchnic nerves. It is suggested that the beneficial results of insulin therapy may be related to undetected subcortical seizures.

(Authors' Abstr.)

Comparison of Psychological Effects of Certain Centrally Acting Drugs in Man

Ten normal volunteers were given various doses of lysergic acid diethylamide (LSD), meperidine, secobarbital, and chlorpromazine. The order of drug administration was a 10×10 Latin square, which included two placebos.

All drugs were administered orally, and the "double-blind" technique was employed throughout. Seventy-five minutes after ingesting the drug, subjects were given a variety of psychological tests, which included intellectual, motor, and perceptual tasks.

The following conclusions were drawn from the data:

The effect of drugs on psychological performance in man are due not only to the specific pharmacological activity of the drug, but also to the specific reactivity of the subject and to an interaction of the two.

There is not a significant correlation between the objective and the subjective psychological effects of a given drug. However, the drugs that produce the greater mean objective effect also produce the greater mean subjective effect.

Two hundred milligrams of secobarbital sodium; 100, 200, and 400 mg. of chlorpromazine hydrochloride, and 50 y and 100 y of lysergic acid diethylamide significantly impair performance on a variety of psychological tests. Meperidine hydrochloride in 50 and 100 mg. doses does not impair performance on the same psychological tests.

LSD had significant effects on intellectual and perceptual tasks but did not cause significant impairment of motor tasks, whereas chlorpromazine and secobarbital affected motor tasks but in general did not cause statistically significant impairment of performance on simple intellectual and perceptual tasks.

Two hundred milligrams of chlorpromazine does not impair performance significantly less than does 200 mg. of secobarbital sodium.

(Authors' Abstr.)

Relationship Between Effects of a Number of Centrally Acting Drugs and Personality

Ten normal young adults were given various doses of chlorpromazine, meperidine, secobarbital, and lysergic acid diethylamide (LSD). The effects of the drugs were determined

by both objective and subjective psychological tests. The Minnesota Multiphasic Personality Inventory was also administered to all the subjects prior to the start of the experiment. Four scales from this test were selected for testing relationships between personality variables and both the objective and the subjective effects of the drugs.

The Depression and Psychoasthenia scales correlated significantly, or almost significantly, with the subjective effects and, to a less extent, with the objective effects of those drugs and dosages that produced significant effects.

These results support a hypothesis that personality plays a role in determining the extent of drug effect.

(Authors' Abstr.)

Effects of Centrally Acting Drugs on Two Tests of Brain Damage

Ten subjects, with a mean age of 20·5 and a mean verbal I.Q. of 110·3, were given low and high doses of one of four drugs or a placebo. Chlorpromazine, LSD-25, meperidine, and secobarbital were administered according to a Latin-square experimental design. The subjects were tested approximately three and a half hours after drug administration on two procedures used for assessing brain damage: the Continuous Performance Test (C.P.T.) and the Wisconsin Card Sorting Test.

None of the measures of performance on the Wisconsin Card Sorting Test show any apparent effect of the drugs. Performance on the C.P.T., however, is significantly poorer under chlorpromazine and becomes even worse as the dose is increased. Although no other drug had a significant effect on C.P.T. performance, it is doubtful if the peak effects of meperidine and secobarbital were measured.

(Authors' Abstr.)

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SYMPOSIUM ON RESERPINE AND CHLORPROMAZINE

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VOL. 80 **BRAIN** MARCH, 1957

Vascular Mechanisms of Birth Injury

A description has been given of the clinical and pathological features of two cases of mental deficiency apparently caused by injury at birth. Both brains showed areas of cortical atrophy in the cerebrum and cerebellum occupying either the boundary zone between two main arterial territories or lying within the fields of supply of individual arteries. These cases illustrate the complex interplay of the vascular mechanisms operative in cerebral birth injury. The boundary zone lesions were considered to be due to a fall below critical level in the systemic blood pressure such as might have occurred in shock associated with birth injury. The second type of lesion was believed to have followed compression of arteries at certain preferential sites caused by the displacement of the brain substance during the process of birth. Such compression would be facilitated by a coincidental lowering of blood pressure and it is significant that in these brains, lesions of both types of distribution occurred together. In the second case, paraventricular softenings of the central white matter and pathological changes in the basal ganglia formed a pattern of cerebral damage attributable to obstruction of the great vein of Galen. In addition, the medial thalamic nucleus contained dense perivascular rings of myelinated fibres which differed from the appearances hitherto reported in *état marbré*.

(Authors' Abstr.)

Vivid Day-dreaming: An Unusual Form of Confusion Following Anterior Cingulectomy

A transient limited confusional state is described as occurring in 8 out of 10 patients after cingulectomy.

The condition consists essentially of an increased vividness of thoughts, dreams and phantasies, so that there is difficulty in distinguishing between mental events and happenings in the external world.

The possible neurological mechanisms involved are briefly discussed.

(Authors' Abstr.)

The Effects of Some Drugs on the Electrical Activity of the Brain

1. The effect of various drugs on the electrical activity of the brain has been studied (*a*) in the conscious animal carrying permanently implanted electrodes, (*b*) in acute preparations sectioned at high spinal or mid-brain level (*encéphale and cerveau isolé* respectively), (*c*) in the barbitone anaesthetized preparation.

2. The importance of studying the effects of drugs in conscious chronic preparations (in which changes in electrical activity can be observed simultaneously with behaviour) is emphasized.

3. In the conscious animal, atropine and physostigmine caused a dissociation between electrical activity and behaviour. Atropine induced slow wave activity. This was similar to that seen in sleep; sleep, however, was never observed. Physostigmine led to an electrical pattern similar to that seen in the alert state, without a corresponding alerting of behaviour. The two drugs were mutually antagonistic.

4. l-Hyoscyamine produced effects similar to those of atropine. d-Hyoscyamine and neostigmine were ineffective, except when the latter drug was given in high enough doses to induce peripheral symptoms.

5. Amphetamine and LSD-25 in the conscious animal led to an alerting of the EEG, and behavioural excitement, there being, in the case of these two drugs, close correlation between electrical activity and behaviour. The effects of amphetamine were independent of the environment, and depended on dosage only. The effects of LSD-25 depended on factors in the environment, as well as upon the drug itself.

6. In the acute preparations the effects of atropine were similar to those seen in the conscious animal, and were still present when either the upper spinal cord, or mid-brain were transected. Amphetamine caused alerting both of behaviour and electrical activity in the *encéphale isolé*, but had no effect on the *cerveau isolé*. LSD-25 had no effect on either of these preparations in the cat, but had some effect on the *encephale isolé* preparation in the monkey.

7. Atropine, physostigmine and LSD-25 modified the electrocortical patterns seen under barbitone anaesthesia. Amphetamine had no effect on barbitone induced activity. The depth of anaesthesia remained apparently unaffected by these drugs.

8. None of the effects described could be correlated either with changes in respiration, or changes in systemic blood pressure.

9. The groupings of the drugs in relation to their effects on electrical activity and on behaviour in the conscious animal, and the levels of section in acute experiment, is discussed. An attempt has been made to relate the findings to the known distribution of the reticular activating system, and the physiology of the brain-stem. It is suggested that three types of receptors are present in the brain. The receptors for LSD-25 may be specially related to the medial collaterals of the great afferent pathways.

10. The possible operation of chemical fields within selected areas of the brain is discussed. (Authors' Abstr.)

Quiactin: an Adjunct in the Treatment of Chronic Psychoses

Quiactin is a tasteless drug of low toxicity which appears pleasant to take. It seems to improve the behavior of irritable patients to an extent that cannot be explained by chance. Its best results seemed to be in cerebral arteriosclerotics, and it is believed that the drug offers much hope in these cases and in the milder psychiatric disorders. The oral dose is 0·8 Gm. to 4·8 Gm. per day.

(Authors' Abstr.)

VOL. 9 EEG CLIN. NEUROPHYSIOL. FEBRUARY, 1957

Studies of Cerebral Circulation in Brain Injury. IV. Ischemia and Hypoxemia of the Brain Stem and Respiratory Center

Concurrent studies of local blood flow, oxygen availability, steady potential (SP) and pH of the respiratory center and carotid body have been made together with continuous recording of blood pressure and respirations. The EPG electrode placed in the wall of the carotid artery records changes in the partial pressure of oxygen of the blood rather than changes in oxygen saturation.

The first effect of anoxic anoxia is stimulation of respiration by the carotid body reflex, continued anoxic anoxia or ischemic anoxia damages the respiratory center, resulting in various patterns of dysrhythmia such as slowed respiration. Cheyne-Stokes breathing, apneusis, gasping and finally respiratory arrest. Incomplete anoxia of the respiratory center causes respiratory arrest due to a state of reversible anoxic neuronal paralysis. In this state of reversible paralysis the respiratory neurones continue to metabolize oxygen but at a reduced rate. Anoxic damage to the respiratory center is associated with local acidity and hyperemia. Whenever respirations fail there is an accompanying injury potential (SP shift) of the respiratory center with respect to the spinal cord white matter.

Seven per cent. CO_2 and oxygen causes hyperpnea which appears to be mediated in the first few seconds by its action on the carotid body and later by its additional action on the respiratory center.

Occlusion of the carotid arteries causes hyperpnea which is mainly due to resultant hypoxemia of the carotid body. There is an increased blood flow in the collateral circulation from the vertebral, basilar and dorsal spinal arteries. Occlusion of the vertebral arteries causes incomplete ischemic anoxia of the brain stem. Respiration continues because the posterior communicating arteries provide a collateral circulation. Additional occlusion of the carotid arteries causes medullary anoxia and respiratory arrest.

Repeated anoxia lowers the threshold of the respiratory neurones to its paralytic effects. Patterns of periodic breathing, resulting from ischemia or anoxemia of the brain under the conditions of these experiments, do not appear to be mediated by periodic fluctuations of oxygen availability of carotid body and respiratory center or rhythmic fluctuations in pH of the respiratory center. They appear to result from anoxic damage to various levels of the brain stem and are reversible.

Brief carbon monoxide breathing lowers the oxygen saturation of the blood without reducing the partial pressure of blood oxygen, the oxygen dissolved in the plasma may provide a critical supply sufficient for the metabolic needs of the respiratory center as the normal oxygen carrying capacity of the blood is slowly restored.

(Author's Abstr.)

A Measurable Neurophysiological Factor of Psychiatric Significance

1. The sedation threshold is a clinical neurophysiological test, which determines the amount of intravenous amobarbital sodium required to produce certain EEG changes. accompanied by slurred speech. Previous investigations have shown the threshold to be related to several significant psychiatric variables, such as degree of manifest anxiety. The purpose of the present study was to further the aim of defining the neurophysiological factor, measured by the sedation threshold, by testing the hypothesis that the threshold is a function of the rate of depressant action of amobarbital on brain activity.

2. An acceptable index of rate of depressant action was required to test the hypothesis. Analysis of data from 399 psychiatric patients and 45 non-patient subjects showed that the amplitude of frontal fast frequency activity, produced by amobarbital, could provide such an index. The mean amplitude at the threshold, which represents a particular level of depressant action, was approximately constant for groups of subjects with different thresholds. The rate of increase of mean amplitude, which could be taken as the index of depressant action, was amenable to quantitative expression as the slope of a rectilinear function, when the logarithm of amplitude was used in calculation. In confirmation of the hypothesis, there was a highly

significant inverse correlation between the sedation threshold and this index of rate of depressant action.

3. In contrast to the sedation threshold, fast frequency amplitude as an absolute value, either before the injection or at threshold, was not significantly related to psychiatric diagnosis. Amplitude at threshold was correlated with amplitude before injection, but neither value was significantly correlated with the sedation threshold.

4. From the conclusion that the sedation threshold is a function of rate of depressant action of amobarbital, it was suggested that it measures a time characteristic of neuronal activity, which is probably an important factor influencing cerebral excitability. The extent to which the sedation threshold findings agree with neurophysiological theories of psychiatric disorder derived from behavioral observation was considered.

(Author's Abstr.)

Difference Between Schizophrenic and Brain-Damaged Groups in Conceptual Aspects of Object Sorting

This was a study of difference in object-sorting behavior between schizophrenic and brain-damaged groups with respect to two conceptual variables—amount of social agreement and order of conceptual classification. It was hypothesized that the brain-damaged group shows a significantly lower order of conceptual classification than does the schizophrenic group.

The variable, social agreement, was scored in terms of the relative publicness-privateness of each conceptual sorting. The second variable, order of classification, was scored in terms of the number of attributes used in the definition. In addition to these two measures, five others were derived from the interaction of the two variables.

An analysis of covariance (controlling for intelligence) indicated that all six measures for which hypotheses were formulated yielded results in the predicted direction and that four of these mean differences were significant at the ·01 level, or better. The greatest F ration was for the closed-open variable, in keeping with the major hypothesis. Differences on all of the measures, except public-private, were greatest between the schizophrenic and brain-damaged groups with the results of the non-psychiatric group falling in between.

(Authors' Abstr.)

VOL. 13 J. CLIN. PSYCHOL. JANUARY, 1957

APRIL

Some Results Obtained by Electrical Stimulation of the Cortex of the Island of Reil in the Brain of the Monkey (Macaca mulatta)

1. The opercularized island of Reil in the lower primates (monkeys) represents the territory of the anterior Sylvian and anterior ectosylvian gyri of non-primates. In addition, monkeys have a fairly extensive non-opercularized island extending rostrally to the fronto-orbital sulcus which apparently is the homologue of the presylvian sulcus of lower forms.

2. The covered insula enlarges through the primate series at the expense of adjacent territory, which includes rostrally that up to the fronto-orbital sulcus, which finally becomes part of the anterior limiting sulcus and the anterior ascending ramus of the lateral fissure in man.

3. As a result of this growth of the insular territory, the whole covered insula of monkeys lies immediately rostral to the central sulcus of the human island of Reil, probably within the short gyrus nearest the former sulcus, and is, by definition, part of the anterior insula of man, which has almost typical agranular isocortex.

4. Although somatic motor movements of the ipsilateral and contralateral face, and contralateral upper and lower extremities were obtained, in that sequence, by stimulating in rostrocaudal order the strip of island cortex covered by the temporal operculum, these results, obtained only with an inductorium in animals under ether narcosis, are not constant enough to advocate the presence of a somatic motor field in the above mentioned region.

5. With ether and various barbiturates as anesthesia, use of a square wave stimulator produced responses only from the area which previously yielded upper extremity movements when the inductorium was used. The nature of these movements with the former stimulator was different. It was bilateral and can be best described as shivering, usually preceded by pil-erection over both shoulders and as far down as the upper two-thirds of the arm. Occasionally, arrest of respiration at inspiration and salivation were also observed from the same and adjacent areas.

(Author's Abstr.)

Differential Growth of the Human Brain

1. The growth of the human brain is analysed by the differential growth equation. By this method the ratios of the specific growth rates (gradients of growth) of 14 dimensions of the brain were determined for the period from the end of the second fetal month to the adult stage.

2. With two exceptions, the ratios of the specific growth rates of these dimensions are constantly proportional throughout the period.

3. Each of the two exceptions, the corpus callosum and the width of the cerebellum, has two gradients of growth separated by an interphase. The interphase for the cerebellum occurs at the end of the 4th fetal month and for the corpus callosum at the end of the 5th fetal month. The interphase for the corpus callosum apparently coincides with the appearance of its full complement of nerve fibers. No morphological factor is known to be responsible for the cerebellar interphase.

4. Alterations in the shape of the brain during ontogeny result from changes in the relative proportionality of its components and the expression of the integration of these changes is the constant ratio between the specific growth rates of these components of the brain.

(Authors' Abstr.)

NOVEMBER

Subcortical Projections from the Temporal Neocortex in Macaca mulatta

Eight Macaca mulatta brains containing surgical lesions of various parts of the temporal neocortex were studied by the aid of the Nauta-Gygax staining technique for degenerative axons. All of the temporal areas studied were found to project to the ventral part of the putamen and to the pulvinar. Additional projections appeared as follows: the convexity of the superior temporal gyrus projects to the medial geniculate body, superior colliculus, intercollicular nucleus, and lateral region of the rostral midbrain tegmentum. Very sparse projections were traced to the pons and inferior colliculus. Projections from the temporal pole pass to the superior colliculus, zona incerta and adjoining parts of lateral midbrain tegmentum. The middle temporal gyrus projects to the tail of the caudate nucleus, to the pretectal area and superior colliculus, and through the inferior thalamic peduncle to the dorsomedial thalamic nucleus. The inferior temporal gyrus projects to the basolateral amygdaloid nuclei, substantia innominata and dorsomedial thalamic nucleus, and to the tail of the caudate nucleus, with minor projections to the reticular thalamic nucleus and zona incerta. Numerous afferents from the middle and inferior temporal convolutions contribute to the anterior commissure.

(Authors' Abstr.)

VOL. 49 J. COMP. PHYSIOL. PSYCHOL. OCTOBER, 1956

DECEMBER

VOL. 50 FEBRUARY 1957

Chlorpromazine (Thorazine) and Reserpine in Residential Treatment of Neuropsychiatric Disorder in Children

In this study of the 74 children treated with reserpine or Thorazine, marked or moderate improvement has occurred in 65 to 81 per cent. of the cases, depending upon type of diagnostic group and the particular drug. It can be concluded that chemotherapy seems to be of definite value as an adjunct in the treatment of schizophrenic children. Although by its action, the

drugs do not alter the schizophrenic process, they can eliminate or reduce to a great extent the intensity of emotional tension and anxiety which makes the patient more amenable to other types of therapy, including psychotherapy. The tranquilizing action of these drugs in the group of other functional-and-personality disorders produced positive changes in behavior patterns. The use of any form of physical restraints has been eliminated completely as well as sedatives; there is no need or indication for electric shock at the present time.

(Author's Abstr.)

JUNE

Studies on Mescaline. V. Electroencephalographic Evidence for the Antagonism Between Mescaline and Chlorpromazine Hydrochloride

1. In a group of 21 epileptics the injection of chlorpromazine hydrochloride served to potentiate the abnormality of the brainwave patterns.

2. Chlorpromazine hydrochloride in 25 schizophrenic patients serves to antagonize the clinical and electroencephalographic effects of mescaline sulfate.

3. Evidence is submitted to suggest the hypothesis that chlorpromazine hydrochloride by its depressant effects on the reticular masses serves to produce an accentuation of paroxysmal and dysrhythmic activity by the removal of the inhibitory activity of the reticular substance.

(Authors' Abstr.)

Further Studies of the Psychological Effects of Frenquel and a Critical Review of Previous Reports

Treatment of schizophrenic patients with oral and intravenous Frenquel failed to confirm claims that this drug has "anti-delusional" or "anti-hallucinatory" effects on such cases. The drug was of no therapeutic value in the patients treated. Even large doses did not modify their behavior or mental symptoms in any consistent way.

A small series of patients with toxic delirium was treated with intravenous Frenquel. No evidence was obtained that the drug has predictable or consistent effects upon the hallucinations or other mental abnormalities associated with such mental disturbances.

Studies on the effects of Frenquel on LSD-25 intoxication in experimental subjects failed to confirm reports that premedication with this drug "blocks" LSD-25 intoxication or that it exerts a specific suppressive effect when given intravenously at the height of the intoxication. In self-experiments with mescaline sulfate, the author found no subjective evidence that premedication with Frenquel modifies the nature or duration of mescaline intoxication.

(Author's Abstr.)

VOL. 20 J. NEUROPHYSIOL. JANUARY, 1957

Shivering as a Result of Brain Stimulation

Electrical stimulation at 21 sites in the brain stem of five cats under light barbiturate anesthesia caused tremor having the characteristics of natural shivering. The positive stimulation sites lay within the lesion-determined "shivering pathway" in the midbrain and pons. The positive hypothalamic stimulation site was located in the medial part of the tuberal hypothalamus, between the mammillothalamic tract and the fornix.

(Authors' Abstr.)

MARCH

Studies on Amygdaloid Nucleus of Cat

1. Stimulations of the amygdala in the unanesthetized cat have been carried out. The responses observed have been autonomic, somatic, and behavioral, this last combining the former two. Electrolytic destruction of the amygdala has been attempted.

2. Pupillary dilatation, salivation, increased gastric acidity and peristalsis, micturition, and defecation have been produced.

3. Ovulation, increase in uterine contractions, and initiation of labor in the pregnant cat, have been observed. Erection and ejaculation were produced in one animal.

4. Somatic activities observed have included turning of the head, facial movements, jaw movements, and tongue movements.

5. Behavioral responses elicited have been a state of alert attention, a reaction of fear, or one of undirected rage.

6. Complete circumscribed destruction of the amygdala was not obtained in any animal. Almost complete and circumscribed, bilateral destructions, however, did not result in ill-tempered animals or in hypersexed animals in any instance.

7. The amygdala has anatomical and functional relations with the hypothalamus which may or may not be the exclusive channel for the expression of amygdala effects. Specific, isolated functional localizations in the amygdala probably do not exist. Patterns of behavioral activity are probably co-ordinated in the amygdala.

(Authors' Abstr.)

Identification of Neurones Giving Burst Response in Isolated Cerebral Cortex

1. An attempt has been made to identify histologically type-B cells (7) of the cat's neurologically isolated cerebral cortex.

2. Cells were detected with the tip of a metal microelectrode pushed slowly through the cortical grey matter, and type-B cells were located by physiological tests.

3. Marks for histological identification were then made in the vicinity of these cells.

4. The results show that the largest type-B cells have their somata in layer V although there are some cells of this type throughout layers II, III, IV and the upper part of VI.

5. The somata of type-B cells are among the largest cell bodies in any layer.

6. Although the connections of the primary type-B cell network appear to lie in layers IV and V, the largest pyramidal cells of layer V are not part of this primary network. Their main function apparently is to convey excitation received from the primary type-B cells out of the cortex.

(Authors' Abstr.)

VOL. 20 J. NEUR. NEUROSURG. PSYCHIAT. FEBRUARY, 1957

Face and Jaw Movements During Epileptiform Discharge in Temporal Regions

In certain primates, repetitive stimulation of one mesial temporal region is followed by ipsilateral facial movements. This intense electrical stimulation induces an after-discharge which can be recorded from the opposite mesial temporal structures. The further electrographic effects of the after-discharge can also be recorded from temporal, parietal, and frontal cortex. It can be established easily at low voltages, and once established it continues for a time. During this period consciousness is altered, the face, jaw, head, and contralateral upper extremity move, and the animal may salivate or lacrimate. Occasionally the ipsilateral grimace occurs before consciousness is altered. There is usually a concomitant tachycardia and an initial inspiratory arrest.

In certain patients, focal epileptiform activity is followed by ipsilateral facial movements. This has been observed in six cases in which the epileptogenic lesion was localized in the mesial temporal region. These ipsilateral movements occurred as initial phenomena in the habitual ictal sequence of these patients. However, facial movements which occur in the ictal progression of a temporal lobe sequence are more commonly bilateral. When the initial movements of the face are one-sided, they may occur on the same side as the significant epileptogenic lesion which lies deep within the mesial temporal region.

(Authors' Abstr.)

Laughter in Epilepsy

Eleven patients with laughter as an epileptiform manifestation have been described. The laughter varied from violent prolonged laughter lasting two minutes or so to giggling and even grinning. The epileptic origin of the laughter was indicated by the lack of any external precipitant, by the nature of the laughter, by concomitant manifestations of epilepsy, and by response to anticonvulsant medication. The clinical and the electroencephalographic picture of these patients showed much variation, but in general indicated the probability of an organic lesion of the brain as the causative factor. The possible role of the hypothalamus in the production of this seizure manifestation has been discussed.

(Authors' Abstr.)

FEBRUARY

Neurologic Guides to Prognosis in Asphyxia and Anoxia

Neurologic examination of patients who have suffered from respiratory arrest or obstruction occurring during or immediately after operation may provide important clues to prognosis. The authors' own experience with such cases has led to the following conclusions, which would appear to apply to patients suffering from cardiac arrest or anoxia from other causes.

1. The occurrence of fixed and dilated pupils and generalized extensor rigidity indicates a severe irrecoverable degree of neuronal damage at the brainstem level, and is, in the authors' experience, incompatible with survival. The appearance of either fixed and dilated pupils or marked generalized extensor rigidity alone is of very grave prognostic significance. Such patients may survive, but serious sequelae may appear.

2. Delayed awakening from anesthesia or asphyxia without abnormal neurologic signs other than mental confusion or impaired memory indicate mild reversible damage at a superficial cortical level and full recovery may be expected.

3. Prognosis is less certain in the intermediate group of patients who show abnormal motor or sensory signs. Survival usually occurs in these patients, and, although there may be recovery which may continue for months, serious sequelae, such as impaired mentality or vision, ataxia, motor or sensory abnormalities, may persist. However, coma that is prolonged more than two or three days is of very serious significance and is often followed by death or serious neurologic after-effects.

(Authors' Abstr.)

VOL. 30 PSYCHIAT. QUART. OCTOBER, 1956

Preliminary Evaluation of a New Phenothiazine Derivative—NP207

1. NP207 appears to have definite beneficial effects in the reduction of tension. It seems to diminish anxiety with fewer side effects than chlorpromazine.

2. Although an insufficient number of patients received both drugs to make a direct comparison, it is the writers' impression that chlorpromazine in equivalent doses is somewhat more effective in reducing anxiety and tension than NP207.

3. NP207 and BOL 148 combined did not show a superior action in the reduction of tension over NP207 alone. Higher doses and a larger series with a different patient group might give better results however.

4. Because of the development with this drug of symptoms resembling retinitis pigmentosa, further research should be undertaken only with extreme caution.

(Authors' Abstr.)

The Management of Side Effects of Chlorpromazine and Reserpine

In the writer's experience, a great number of patients fail to show improvement with either chlorpromazine or reserpine because the dosage is insufficient, or too little is given when side effects appear, or therapy is discontinued because of the side effects. About 50 per cent of such patients can receive proper dosages when the side effects are counterbalanced symptomatically; and such patients have shown marked improvement or have recovered. It is strongly, felt, therefore, that great attention should be placed on the neutralization or palliation of side effects, through ancillary medication and nursing techniques—rather than abandon therapy or reduce dosage below therapeutic levels. This is particularly in view of the fact that—save in few and far-between instances—the side effects are merely bothersome, not injurious, and severe complications are few.

It is recognized that side effects cannot be overcome in every instance. Yet the writer's experience has shown that in general they can be mitigated, at least to the point of making them bearable. By this means, more patients may expect relief from their psychiatric problems

and the drugs may be used more effectively and economically. The implications of this are of extraordinary importance, not only for intramurally-treated patients, but for those undergoing ambulatory and outpatient treatment.

No attempt has been made here to cover all the known side effects of the tranquillizing drugs, but the more general or significant ones have been described and their handling outlined. Other solutions of these problems are, of course, possible and conceivable, and depend only on the ingenuity exercised by the individual physician. The dosages given are only illustrative, both those of the drugs and of the corrective medication. It must be emphasized that dosage depends principally on the individual response and not on the medication *per se*.

(Author's Abstr.)

Anesthesia. LIII. Effect of Alcohols and Acetaldehyde on Oxidative Phosphorylation in Brain

1. Alcohol and its homologues up to *n*-butanol do not uncouple oxidative phosphorylation from respiration at concentrations producing acute intoxication or narcotic activity *in vivo*.

2. A limited uncoupling action was observed for *n*-pentanol in high concentration.

3. Tribromoethanol solution is another anesthetic alcohol not eliciting significant uncoupling activity.

4. These results are interpreted as further evidence against the uncoupling of oxidative phosphorylation from respiration as a common mechanism of action of anesthetic and hypnotic agents.

5. Acetaldehyde produces a limited degree of uncoupling, but does so in concentrations approximating those occurring *in vivo* both normally and following the disulfiram-alcohol reaction.

6. The implications of these findings for the mechanism of the neuropharmacologic actions of alcohol and acetaldehyde are discussed.

(Authors' Abstr.)