Bibliography and Epitome

VOL. 31 ACTA PSYCHIAT. NEUR. SCAND. 1956

Adrenocortical and Thyroid Function in Periodic Catatonia. *Gume, L.-M., and Gemzell, C. A.* 367
Enuresis. I. *Hallgren, B.* 379
Enuresis. II. *Hallgren, B.* 405
A Comparison between Combined Reserpine-Chlorpromazine and Chlorpromazine Therapies in Psychiatry. *Hormia, A.* 437
An Attempt at Evaluating the Contents of the Concept of Actual Neurosis. *Højer-Pedersen, W.* 447
Colorimetric Estimation of Succinic Dehydrogenase Activity in the Rabbit Brain with Tetrazolium Salt. *Kawakita, Y.* 459
Adrenalin- and Mecholyl Test Performed in Schizophrenia and Schizophreniform States. *Laane, C. L.* 467

VOL. 61 AM. J. MENT. DEFIC. JANUARY, 1957

Reserpine and Chlorpromazine in Hyperactive Mental Defectives. *Horenstein, S.* .. 525
The Excretion of β-Aminoisobutyric Acid in Normal, Mongoloid and Non-Mongoloid Defective Children. *Wright, S. W., and Fink, K.* 530
Infantile Spastic Hemiplegia Intelligence, and Age of Walking and Talking. *Perlstein, M. A., and Hood, P. N.* 534
The Concept Propfschschizophrenia and its Prognosis. *Lanzkron, J.* 544
The Performance of Schizophrenic, Retarded and Normal Children on the Bender-Gestalt Test. *Goldberg, F. H.* 548
A Comparison of Two Types of Learning in Mental Defectives. *Sloan, W., and Berg, D. A.* 556
Ethnocentrism and Intolerance of Ambiguity in Mentally Retarded Children. *Rosenblum, S.* 567
The Relationship of Auditory Memory Span to Learning Ability in High Grade Mentally Retarded Boys. *Keller, J. E.* 574
Digit Span and Anxiety. *Callahan, R. J., and Keller, J. E.* 581

VOL. 113 AM. J. PSYCHIAT. DECEMBER, 1956

Genetic Principles in Human Populations. *Muller, H. J.* 481
The Molecular Basis of Genetics. *Panting, L.* 492
The Genetics of Human Behaviour. *Kallmann, F. J.* 496
Discussion of the Genetics Symposium. *Brosin, H. W.* 502
Discussion of the Genetics Symposium. *Glass, B.* 504
Letter from Germany. *Roeder, F. D.* 506
Neurophysiologic and Pharmacologic Influences on Experimental Neuroses. *Masserman, J. H., and Pechtel, C.* 510
Therapeutic Results in Mental Hospitals with a Minimum of Professional Personnel. *Bartemeier, L. H.* 515
The Problem of Ambulatory Schizophrenics. *Zilboorg, G.* 519
Anxiety Problems within Cultural Settings. *Appel, K. E.* 526
*The Ataractic Drugs. *Bones, H. A.* 530
*A Two-year Evaluation of Chlorpromazine in Clinical Research and Practice. *Malitz, S., et al.* 540
*Methyl-Phenidylacetate Hydrochloride (Ritalin) in the Treatment of Chronic Schizophrenic Patients. *Carey, B., et al.* 546
Ways of American Psychiatry. *Rocha, J. S.* 548
Advances in Management and Treatment of European Mental Hospitals. *Kalinoswsky, L. B.* 549

The Ataractic Drugs: the Present Position of Chlorpromazine, Frenquel, Pacatal, and Reserpine in Psychiatric Hospital

The ataractic drugs are so called from their ability to produce ataraxy: freedom from confusion and anxiety. In a veterans' psychiatric unit of 550 beds with a high rate of admissions and discharges, chlorpromazine and reserpine have been intensively studied during the past 2 years and since June, 1955, Frenquel has been given to 130 patients, and Pacatal to over 250, in an effort to clarify the indications for these ataraxics in the treatment of acute and chronic psychoses.

The experiences with Frenquel are described in some detail as the originally hopeful and eventually disillusioning results obtained may explain many ambiguous findings in this

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complex field of research. Frenquel appears to have anti-hallucinatory and physically tonic effects in a small minority of regressed schizophrenics but to be of no value in the treatment of acute psychoses. Reserpine has also failed to fulfil earlier expectations. It is now reserved for the tranquillization of arteriosclerotics and as an adjuvant in the psychotherapy of some withdrawn schizophrenics.

Pacatal, a phenothiazine derivative recently developed in Europe, and chlorpromazine are virtually interchangeable and synergistic. Pacatal is almost twice as strong a tranquillizer but a weaker hypnotic. It is mildly euphoriant and strongly parasympatholytic unlike chlorpromazine, a sympatholytic and depressant. Both are indicated in the symptomatic relief of psychomotor excitation, aggression, destructiveness, restlessness, and tension in acute and chronic psychoses. A combination of both, in which their mutually antagonistic autonomic effects reduce the incidence of complications and abolish the Parkinsonian syndrome, is yielding promising results.

In this study these drugs have significantly reduced the need for E.C.T. and lobotomy without replacing these valuable methods of treatment. The seclusion of disturbed patients has been reduced to one-tenth. Since July, 1955, insulin coma therapy has been replaced by group psychotherapy using ataraxics as adjuvants. Over twice the number of patients can be treated, so far with better results. The discharges during 1955 outnumbered the admissions; the hospital atmosphere is calmer, and there is increased confidence and optimism. These latter factors cannot be ignored.

Alone, ataraxics merely modify symptoms but in conjunction with psychotherapy they open up wide vistas of therapeutic promise.

(Author's Abstr.)

A Two-year Evaluation of Chlorpromazine in Clinical Research and Practice

In conclusion, it is believed that chlorpromazine has established itself as a useful therapeutic tool in the treatment of mental illness. It is a relatively safe drug, and although the side-effects are many, serious or permanent sequelae are almost unknown. In regard to its therapeutic effect in our case material much is left to be desired. Its range of application appears to be narrow, being most effective in agitated, hyperactive, and overtly anxious patients, with much more limited value in depression, or with obsessive patients manifesting little or no increase in motor function. It is palliative rather than curative. It can intensify anxiety and precipitate depression and psychotic symptoms as well as alleviate them. Its major advantage lies in its tranquillizing action without accompanying marked drowsiness or confusion. Its value as an adjunct to psychotherapy is still to be evaluated.

Chlorpromazine has been a major force in firmly launching us into the era of psychopharmacology. We are still suffering, however, from all the uncertainties and hesitation of a pioneer venture. This should not deter us from continued investigation and progress.

(Authors' Abstr.)

Methyl-Phenidylacetate Hydrochloride (Ritalin) in the Treatment of Chronic Schizophrenic Patients

In this group of 50 chronic schizophrenic patients, half of whom received Ritalin and half an identical appearing placebo the Ritalin was without demonstrable effect. Six of those on Ritalin showed a decrease in appetite, abdominal discomfort, and weight loss during the test.

(Authors' Abstr.)

VOL. 76 ARCH. NEUR. PSYCHIAT. DECEMBER, 1956

Studies on Headache. *Richler, E., et al.* 571
Hydranencephaly. *Alexander, E., jun., et al.* 578
Relationship Between the Wernicke and the Korsakoff Syndrome. *Malamud, N., and Skillicorn, S. A.* 585
Early Ambulation and Psychotherapy for Treatment of Closed Head Injury. *Müller, R., and Naumann, B.* 597
Lipoprotein Patterns of Spinal Fluid Obtained by Electrophoresis. *Smith, J. K., et al.* 608
*The Time Sense. *Lhamon, W. T., and Goldstone, S.* 625
*Glutathione Levels in Mental and Physical Illness. *Martens, S., et al.* 630
*Studies of the Role of Ceruloplasmin and Albumin in Adrenaline Metabolism. *Leach, B. E., et al.* 635
Receptor Preferences in Schizophrenic Children. *Goldfarb, W.* 643
*EEG During E.C.T. with Succinylcholine. *Piekenbrock, T. C., et al.* 653
Discharge and Readmission Among Mental Hospital Patients. *Wanklin, J. M., et al.* 660
Physiologic Stress Response Evaluation by Focused Interviewing, *Cohen, S. I., et al.* 670
*Chlorpromazine and Hepatic Function. *Kinross-Wright, V., and Moyer, J. H.* .. 675

The Time Sense

Thirty-seven schizophrenic patients were compared with 41 control subjects with respect to their estimation of one clock second's duration. It was found that the group of patients had a significantly smaller second estimation point (SEP) when tested by a "passive" method than did the control group. Patients and control subjects were surprisingly stable in their

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estimates. The effect of providing information of the actual duration of a clock second was studied in both groups. The relation of these findings to the psychopathology of schizophrenia is briefly discussed.

(Authors' Abstr.)

Glutathione Levels in Mental and Physical Illness

The authors' findings of lower levels of reduced GSH in schizophrenics than in normals confirm reports of other workers. This finding is not specific for schizophrenic patients, since we find it also in patients with various intercurrent diseases. There appears to be a relationship between lower GSH levels and high levels of serum globulin. These results are compared with those which we reported earlier regarding the speed of adrenaline oxidation. In that study, many patients without psychosis, but with other disease processes, similarly showed changes characteristically seen in psychotics. In some instances, however, where adrenaline metabolism was altered, the GSH levels were in the normal range. The question whether the same enzymatic system may affect both indicators, or whether they are more indirectly related to each other, is discussed. Further explorations of the role of ceruloplasmin and/or closely related substances in association with these biochemical abnormalities are presented in a separate paper.

(Authors' Abstr.)

Studies of the Role of Ceruloplasmin and Albumin in Adrenaline Metabolism

In this study the authors have attempted to isolate those substances which influence the speed of oxidation of adrenaline as determined in an *in vitro* test. Data presented indicate that ceruloplasmin, a copper globulin, is the important oxidizing substance and that albumin is an active inhibitor of this process.

(Authors' Abstr.)

EEG During Electroconvulsive Therapy with Succinylcholine

Electroencephalographic tracings were made on 15 psychiatric patients during electroconvulsive therapy premedicated with thiopental sodium and atropine and immobilized with succinylcholine.

The electroencephalographic changes consisted in the appearance of (*a*) high-voltage slow waves mixed with fast activity after thiopental sodium and atropine; (*b*) a transitory burst of muscle after succinylcholine, followed by disappearance of all muscle activity; (*c*) fast activity, followed by spike and wave patterns with a strong 3-per-second spike-dome component following electroconvulsive treatment; (*d*) a flattening of all activity with or without administration of oxygen 30 seconds after stimulation; and (*e*) irregular high-voltage slow waves during the stupor period.

(Authors' Abstr.)

Chlorpromazine and Hepatic Function

The hepatic function of 30 medical and 33 psychiatric patients under treatment with chlorpromazine was studied.

No changes were found, and it is considered that routine liver function tests are of no value for predicting the development of hepatotoxicity.

The etiology of jaundice following chlorpromazine and other drugs is discussed, and two case histories are presented.

(Authors' Abstr.)

VOL. 79 **BRAIN** DECEMBER, 1956

The Babinski Plantar Response. *Walshe, F. M. R.* 529
Cough Headache. *Symonds, C.* 557
Cerebral Dominance in Sinistrals. *Ettlinger, G., et al.* 569
Disorders of Laughter due to Brain Lesions. *Ironside, R.* 589
A New Congenital Non-progressive Myopathy. *Shy, G. M., and Magee, K. R.* .. 610
Cysticercosis of the Posterior Fossa. *Bickerstaff, E. R., et al.* 622
Observations on the Prevalence of Multiple Sclerosis in Northern Scotland. *Sutherland, J. M.* 635
Habituation of the Arousal Reaction. *Sharpless, S., and Jasper, H.* 655

VOL. 17 **DIS. NERV. SYST.** DECEMBER, 1956

The Arnold-Chiari Malformation without Spinal Dysraphia. *Jackson, I. J., and Hoffman, G. T.* 375
Monopolar E.C.T. Coma for "Hard-core" Cases. *Epstein, J., and Campden-Main, B. C.* 379
N-Methyl-A,A-Methylphenylsuccinimide in Psychomotor Epilepsy. *Cordoba, E. F., and Strobos, R. R. J.* 383
Medicolegal Aspects of the Doctor-Patient Relationship. *Siegal, L. J.* 386
Neurotic Aversion to Kissing. *Bergler, E.* 391
Clinical Evaluation of Ritalin. *Natenshon, A. L.* 392

https://doi.org/10.1192/bjp.103.432.682 Published online by Cambridge University Press

VOL. 59 FOL. PSYCHIAT. NEUR. NEUROCHIR. NEERL. AUGUST, 1956

Steering under Abnormal Circumstances. *Bok, S. T.* 303
Hypothalamic Syndromes in General and Disturbances in the Water Regulation in Particular. *Biemond, A.* 338
Relationship Between the Central Nervous System and the Thyroid Gland. *Querido, A.* 359
Temperature and Heat Regulation. *Verbiest, H.* 363
Some Functions of the Hypothalamic-hypophysial System in Relation to the Pathology. *Prick, J. J. G.* 408

OCTOBER

Some Remarks on a Common Disorder "Occupational Inhibitions". *van Dijk, W., and Kuiper, P. C.* 485
A New Psychological Approach to the Concept of the "Epileptic Personality". *Ceha, M. M. T., and Boeke, P. E.* 499
Some Remarks on the So-called "Spastic" Gait. *Tan, B. K.* 508
Pathological Jealousy and Jealous Delusions. *Tiggelaar, J.* 522

VOL. 54 GENET. PSYCHOL. MONOGR. NOVEMBER, 1956

The Influence of Social Context on Impulse and Control Tendencies in Preadolescents. *Zuk, G. H.* 117
Tender-mindedness versus Tough-mindedness in Psychology. *Winthrop, H.* 167
A Method for the Comparison of Groups. *Schaw, L. C., and Henry, W. E.* 207

VOL. 37 INTERNAT. J. PSYCHO-ANAL. 1956

The Development of the Ego Concept in Freud's Work. *Hartman, H.* 425
Re-evaluation of the Process of Working Through. *Greenacre, P.* 439
On Some Vicissitudes of Insight in Psycho-analysis. *Kris, E.* 445
The Role of Identification in Psycho-analytic Procedure. *Groot, J. L.* 456
Some Remarks on the Role of Speech in Psycho-analytic Technique. *Loewenstein, R. M.* 460
The Nature and Function of the Analyst's Communication to the Patient. *Rycroft, C.* 469

VOL. 105 J. COMP. NEUR. SEPTEMBER, 1956

Research on the Regeneration of the Spinal Cord in the Cat Submitted to the Action of Pyrogenous Substances (5 OR 3895) of Bacterial Origin. *Arteta, J. L.* 171
Action of the Pyrogenous Substances (5 OR 3895) on the Regeneration of the Peripheral Nerve. *Arteta, J. L.* 185
*A Study of the Red Nucleus in the Rhesus Monkey. Anatomic Degenerations and Physiologic Effects Resulting from Localized Lesions of the Red Nucleus. *Carpenter, Malcolm B.* 195
Components of Splanchnic and Intermesenteric Nerves. *Kuntz, Albert* 251
The Neural Pattern of the Epiglottis. *Feindel, William* 269
The Central Tegmental Bundle. An Anatomical and Experimental Study in the Monkey. *Bebin, Jose* 287
Myelin Sheath During Degeneration and Regeneration. II. Histochemistry. *Noback, Charles R., and Reilly, James A.* 333

A Study of the Red Nucleus in the Rhesus Monkey. Anatomic Degenerations and Physiologic Effects Resulting from Localized Lesions of the Red Nucleus

An attempt was made to produce localized stereotaxic lesions of the red nucleus in a series of 25 rhesus monkeys in order to study the resulting physiologic effects and anatomic degenerations. Animals were carefully observed before and after surgery; cinematographic records were taken of noteworthy physiologic phenomena. Serial sections of the brains and portions of the spinal cords of these animals were stained according to the Marchi technique; every 10th section was mounted.

Localized red nucleus lesions were produced in 12 monkeys; such lesions were considered worthy of detailed analysis in 10 animals. Lesions were considered unilateral if more than 15 per cent. of the total volume of the red nucleus was destroyed on one side and bilateral if more than 15 per cent. of the volume of the red nucleus was destroyed on each side. According to this criterion, 5 animals had unilateral lesions and 5 had bilateral lesions. Percentile volumes of the red nucleus destroyed in these animals varied from 1·7 to 51 per cent. The percentile volumes of the red nucleus destroyed in animals with unilateral lesions averaged 26·6 per cent. and 27·2 per cent. in those with bilateral lesions. The following conclusions were drawn:

1. Fibers originating in the red nucleus project ipsilaterally to the arcuate nucleus of the thalamus via the thalamic fasciculus. Such fibers appear to arise from both the rostral and caudal halves of the red nucleus.

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2. Fibers originating in the red nucleus project to the globus pallidus via the ventral division of the ansa lenticularis. These fibers arise from both rostral and caudal halves of the red nucleus and appear to be mainly uncrossed.

3. Fibers originating in the caudal half of the red nucleus project to the ipsilateral subthalamic nucleus.

4. The possibility that some fibers originating in the red nucleus project to the contralateral arcuate nucleus of the thalamus, the globus pallidus and the subthalamic nucleus could not be excluded.

5. As a result of localized lesions in the red nucleus ascending Marchi degeneration also can be followed into the lateroventral nucleus of the thalamus and into the globus pallidus via the dorsal division of the ansa lenticularis on the same side as the lesion. Degeneration in these sites is the same as that produced by lesions of the opposite brachium conjunctivum below the red nucleus.

6. Lesions of the red nucleus frequently produce transient tremor (simple and ataxic), ataxia and cerebellar asynergia which disappears without residuum.

7. Bilateral lesions of the red nucleus provoked marked hypokinesis which is enduring, but does not impair the quality of motor performance.

8. Unilateral or asymmetrical lesions of the red nucleus may provoke rotation and tilt of the head to the side opposite the lesion (or the larger lesion in the case of bilateral lesions). This physiologic effect may be of brief duration or persist until death or sacrifice.

9. Neither tremor, ataxia nor cerebellar asynergia phenomena of an enduring nature result from well localized lesions of the red nucleus, although significant portions of the crossed ascending limb of the brachium conjunctivum are interrupted by such lesions.

The hypothesis is presented that tremor (simple and ataxia), ataxia and cerebellar asynergic phenomena do not result from lesions interrupting the crossed ascending limb of the brachium conjunctivum at the level of the red nucleus or above.

(Author's Abstr.)

VOL. 19 J. NEUROPHYSIOL. NOVEMBER, 1956

*Somatic Afferent Areas I and II of Dog's Cerebral Cortex. *Hamny, T. P., et al.* .. 485
*Role of Auditory Cortex in Discrimination Requiring Localization of Sound in Space. *Neff, W. D., et al.* 500
The Direct Cortical Response. *Ochs, S.* 513
Ventral Root Discharge in Response to Vestibular and Proprioceptive Stimulation. *Andersson, S., and Gernandt, B. E.* 524
Sensory and Motor Localisation in Cerebral Cortex of Porcupine. *Lende, R. A., and Woolsey, C. N.* 544
Suprasegmental Inhibition of an Autonomic Reflex. *Wang, G. H., and Brown, V. W.* 564
Nature of Dendritic Potentials and Synaptic Mechanisms in Cerebral Cortex of Cat. *Purpura, D. P., and Grundfest, H.* 573

Somatic Afferent Areas I and II of Dog's Cerebral Cortex

1. Somatic afferent areas I and II (SI and SII) of the cerebral cortex of the dog have been mapped by the evoked potential method, using mechanical movement of hairs or light pressure to the skin as stimuli.

2. The body surface is so represented in SI that the animal appears to be lying with tail and postaxial thigh on the medial wall of the hemisphere and the preaxial thigh on the dorsal surface; the back of the animal and the occipital aspect of the head fall along the caudal margin of the area, toward the visual cortex; the ventral surface of the trunk, the apices of the limbs and the snout are directed rostralward. There is continuity of foci for trunk, neck and face, but not for tail and trunk. In general, the arrangement is similar to that previously described for the rat. The area is activated only by stimulation of the contralateral half of the body, except for a special portion of SI, the ipsilateral face area, which forms the rostral part of the face area.

3. SII has been found to possess a high degree of somatotopic differentiation, in contrast with earlier reports for this area in other species. The localization pattern is such that the back of the animal lies inferiorly, along the dorsal border of the insula, while the limbs and face extend upward over the anterior ectosylvian gyrus toward SI, with the snout most rostral and the foot most caudal. The area can be activated by stimulation of both sides of the body, responses to ipsilateral stimulation being approximately half as large as those to contralateral stimulation.

4. Tunturi's third auditory area lies within the face subdivision of SII.

(Authors' Abstr.)

Role of Auditory Cortex in Discrimination Requiring Localization of Sound in Space

1. Cats were trained to make a response requiring localization of sound in space. Lesions were then made in the cortical projection areas of the auditory system.

2. After bilateral ablation of AI and, in some cases, of AII and Ep, a severe deficit in performance was found. In contrast, response to visual cues in the same situation was readily

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learned, and control animals with ablation of non-auditory cortex retained the sound-localization habit and showed no deficit in performance.

3. Performance improved when the experimental situation was changed so that less accurate localization of sound in space was required and less chance was allowed for a change from the initial direction of a response.

4. Several hypotheses are suggested as to the role of the auditory projection areas in the control of behavior involving localization of sound in space.

(Authors' Abstr.)

VOL. 13 J. NEUROSURG. NOVEMBER, 1956

Cephalic Bruits in Children. *Dodge, H. W., jr.* .. 527
The Diagnosis, Treatment and Prognosis of Tumors Affecting the Spinal Cord in Children. *Grant, F. C., and Austin, G. M.* .. 535
Communicating Hydrocephalus from Subarachnoid Bleeding. *Foltz, E. L., and Ward, A. A., jr.* .. 546
Safe Angiography. *Segelov, J. N.* .. 567
Infarctions Simulating Brain Tumours in the Posterior Fossa. *Lindgren, S. O.* .. 575
Epileptic Effects of Intracisternal Alumina Cream in Monkeys. *Chusid, J. G., et al.* 582
The Use of Phenolsulphonphthalein in the Clinical Evaluation of Hydrocephalus. *Bering, E. A., jr.* .. 587
Selective Partial Neurectomy in Hemifacial Spasm and the Electrophysiologic Selection of Patients. *Nosik, W. A., and Weil, A. A.* .. 596
Benign Tumors at the Foramen Magnum: Surgical Considerations. *Dodge, H. W., jr., et al.* .. 603
The Results of Surgical Treatment of Intracranial Aneurysms as Demonstrated by Progress Arteriography. *Mount, L. A., and Taveras, J. M.* .. 618
The Use of Sodium Diacetrizoate in Cerebral Angiography. *Dunn, J., jr., et al.* .. 627
Application of Monomolecular Filter Tubes in Bridging Gaps in Peripheral Nerves and for Prevention of Neuroma Formation. A Preliminary Report. *Campbell, J. B., et al.* .. 635

VOL. 14 JANUARY, 1957

The Use of Epidural Anesthesia for Excision of the Lumbar Disc. Report of 125 Cases. *Tice, W. P.* .. 1
The Role of Perineurial Sacral Cysts in the Sciatic and Sacrococcygeal Syndromes. A Review of the Literature and Report of 9 Cases. *Abbott, K. H., et al.* .. 5
*Acetylcholine and Serotonin in the Spinal Fluid. *Sachs, E., jr.* .. 22
Intradural Lipomas of the Spinal Cord. With Particular Emphasis on the "Intramedullary" Lipomas. *Caram, P. C., et al.* .. 28
Experimental Observations on the Prevention of Seizures by Intravenous Procaine Injections. *French, J. D., et al.* .. 43
Variations in the Spinothalamic Tract in Man. *Voris, H. C.* .. 55
The Thoracic Herniated Intervertebral Disc Syndrome. *Kite, W. C., jr., et al.* .. 61
A Note on the Treatment of Involuntary Movements of the Arm by Resection of the Brachial Plexus. *Bridge, C. J., and Horrax, G.* .. 68
Fatal Brain-Stem Shift Following Hemispherectomy. *Cabieses, F., et al.* .. 74

Acetylcholine and Serotonin in the Spinal Fluid

1. Spinal fluid acetylcholine and serotonin determinations have been done on a series of 140 patients suffering from head injuries and brain tumors and a variety of other neurologic disorders.

2. Both acetylcholine and serotonin, as well as another unidentified substance, have been found in a large percentage of these cases. Serotonin has not been reported previously in the spinal fluid of man.

3. Comparable studies on experimentally concussed animals have also been reported.

(Author's Abstr.)

VOL. 25 J. PERSONAL. SEPTEMBER, 1956

Effects of Anxiety, Stress and Task Variables on Reaction Time. *Farber, I. E., and Spence, K. W.* .. 1
Past Experience and Present Personality Disposition as Determinants of Selective Auditory Memory. *Davids, A.* .. 19
The Effects of Stuttering Behavior and Response Set on Recognition Thresholds. *Spielberger, C. D.* .. 33
Dynamic Systems, Perceptual Differentiation and Intelligence. *Livson, N., and Krech, D.* .. 46
Random versus Systematic Distribution of Information in Communication Nets. *Shaw, M. E.* .. 59

https://doi.org/10.1192/bjp.103.432.682 Published online by Cambridge University Press

A Further Study of Infantile Handling and Adult Avoidance Learning. *Levine, S.* .. 70
The Judgment of Ambiguous Stimuli as an Index of Cognitive Functioning in Aging. *Korehin, S. J., and Basowitz, H.* 81
Self-Ratings and T.A.T. *Child, I. L., et al.* 96

VOL. 20 J. PROJ. TECHN. DECEMBER, 1956

Social Interest, an Adlerian Rationale for the Rorschach Human Movement Response. *Ansbacher, H. L.* 363
Prognostic Significance of the Under-productive Rorschach. *Bloom, B. L.* 366
TAT as a Measure of the Hunger Drive. *Epstein, S., and Smith, R.* 372
A Study of the Reliability in Human Figure Drawings. *Graham, S. R.* 385
A Study of Ego Identification by Means of an Index of Identification Derived from Six TAT Cards. *Groh, L. S.* 387
Two Dimensions of Test Structure in Rorschach-like Projective Tests. *McFarland, R. L.* 398
Motion Perception, Time Perspective and Creativity. *Miner, J. B.* 405
Rorschach Changes during Psychoanalysis. *Mintz, E., et al.* 414
The Projection of Hostility on the Rorschach and as a Result of Ego-threat. *Murstein, B. I.* 418
Insight Test Prognosis in Successful and Unsuccessful Rehabilitation of the Blind. *Sargent, H. D.* 429
The TAT Aggressive Content Scale. *Stone, H.* 445
Neurotic Depressives' and Alcoholics' Oral Rorschach Percepts. *Wiener, G.* 453

VOL. 44 J. SOC. PSYCHOL. NOVEMBER, 1956

Some Aspects of Personality Structuring in India (Hindu) Social Organization. *Asthana, H. S.* 153
Factor Analysis of Roles Patients Take in Therapy Groups. *Giedt, F. H.* 165
A "Culture and Personality" Study Based on a Comparison of Rorschach Performance. *Siegman, A. W.* 173
The Non-projective Aspects of the Rorschach Experiment. I. *Zubin, J.* 179
The Non-projective Aspects of the Rorschach Experiment. II. *Werner, H., and Wapner, S.* 193
The Non-projective Aspects of the Rorschach Experiment. III. *Haufmann, E.* .. 199
The Non-projective Aspects of the Rorschach Experiment. IV. *Gilson, J. J.* 203
The Non-projective Aspects of the Rorschach Experiment. V. *Singer, J. L.* 207
A Modified Interpretation of Thurstone's Flexibility of Closure Factor. *Keehn, J. D.* 215
Sociometric Status and Supervisory Evaluation of Institutionalized Mentally Deficient Children. *Clampitt, R. R., and Charles, D. C.* 223
Accuracy in Judging Emotional Expressions as Related to College Entrance Test Scores. *Weisgerber, C. A.* 233
The Role of Emotion in Prejudice. *Cooper, J. B., and Singer, D. N.* 241
Social Interactions of Rhesus Monkeys. I. *Miller, R. E., and Murphy, J. V.* 249
A Shortened "Basic English" Version (Form C) of the PF Questionnaire. *Cattell, R. B.* 257
College Environment, Personality and Social Ideology of Three Ethnic Groups. *Brown, D. R., and Bystryn, D.* 279

VOL. 6 NEUROL. DECEMBER, 1956

Large Intracranial Aneurysm Producing Panhypopituitarism and Frontal Lobe Syndrome. *Gallagher, P. G., et al.* 829
An Early Description of the Gerstmann Syndrome. *Benton, A. L., and Meyers, R.* .. 838
Quantitative Assessment of Motor Function in Cerebral Palsy. *Millichap, J. G., and Hadra, R.* 843
On Neurologic Terminology, Eponyms and the Lasègue Sign. *Wartenberg, R.* .. 853
Changes in the Glycoproteins of the Cerebrospinal Fluid in Neurologic Diseases. *Apostol, R. R., et al.* 859
Hearing and Speech in Infantile Hemiplegia Before and After Left Hemispherectomy. *Goldstein, R., et al.* 869
Familial Cerebello-olivary Degeneration with Late Development of Rigidity and Dementia. *Carter, H. R., and Sukarajana, C.* 876

VOL. 19 PSYCHIAT. NOVEMBER, 1956

Human Ego Functions in the Light of Animal Behavior. *Weigert, E.* 325
The Rating and Group Dynamics of the Psychiatric Staff Conference. *Whitman, R. M.* 333
Masculine Aspirations in Women. *Ovesey, L.* 341
Countertransference in the Psychotherapy of Marriage Partners. *Bird, H. W., and Martin, P. A.* 353
The Locus of Power in a Large Mental Hospital. *Cumming, E. and J.* 361
An Operational Conception of Psychotherapy. *Glad, D. A.* 371
Confabulation as a Social Process. *Weinstein, E. A., et al.* 383

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VOL. 25 PSYCHOANAL. QUART. OCTOBER, 1956

River Symbolism. Part I. *Niederland, W. G.* 469
Clinical Manifestations of Ambivalence. *Brody, M. W.* 505
The Management of an Erotized Transference. *Rappaport, E. A.* 515
General Aspects and Implications of Introjection. *Bychowski, G.* 530
The Psychological Structure of Space with Some Remarks on Robinson Crusoe. *Berne, E.* 549
The Relationship Between Man and Dog. *Heiman, M.* 568

VOL. 18 PSYCHOSOM. MED. 1956

Social Class Prevalence and Distribution of Psychosomatic Condition in an Urban Population. *Rennie, T. A. C., and Srole, L.* 449
Some Influences of an Experimental Situation on the Psychotherapeutic Process. *Watson, P. D., and Kanter, S. S.* 457
Psychogenic Factors in Essential Hypertension. *Moses, L., et al.* 471
Psychological Factors Related to Results of Subtotal Gastrectomy. *Weiner, I.* 486
Psychoanalytic Psychotherapy in Raynaud's Disease. *Millet, J. A. P.* 492
Influence of Hindu Culture and Social Customs on Psychosomatic Disease in India. *Gupta, N. N.* 506

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