

Bulletin of the



**University of Minnesota Hospitals
and
Minnesota Medical Foundation**



**Convulsive Disorders
In Adults**

BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
and
MINNESOTA MEDICAL FOUNDATION

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UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

October 11 - 16, 1948

No. 217

Monday, October 11

- 9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; Interns' Quarters, U. H.
- 8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.
- 10:00 - 12:00 Neurology Ward Rounds; A. B. Baker and Staff; Station 50, U. H.
- 11:00 - 11:50 Roentgenology-Medicine Conference; Staff, Veterans' Hospital.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.
- 11:00 - 11:50 Physical Medicine Seminar; The Anatomy of the Knee; Glen Gullickson; E-101, U. H.
- 12:00 - 1:00 Physiology Seminar; 214 M. H.
- 12:15 - 1:20 Obstetrics and Gynecology Journal Club; M-435, U. H.
- 12:30 - 1:20 Pathology Seminar; Infectious Mononucleosis; Maynard Cohen; 104 I. A.
- 12:30 - 1:50 Surgery Grand Rounds; A. A. Zierold, Clarence Dennis and Staff; Minneapolis General Hospital.
- 1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.
- 2:00 - 3:00 Surgery Problem Case Conference; C. Dennis and Staff; Small Class Room, General Hospital.
- 3:00 - 5:00 Kellogg Lecture; The Anemias in their Diagnosis and Treatment; Malcolm M. Hargraves; Chapel, CCS.
- 4:00 - 6:00 School of Public Health Seminar; Environmental Sanitation in Alaska; H. A. Whittaker; 113 MeS.
- 5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.
- 5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

Tuesday, October 12 - HolidayWednesday, October 13

- 8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.
- 8:30 - 12:00 Neurology Rehabilitation and Case Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.
- 8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans' Hospital.
- 11:00 - 12:00 Pathology-Medicine-Surgery Conference; Myocardial Infarction, Hypochloremia; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.
- 1:00 - 3:00 Kellogg Lecture; Hemopoiesas; Hal Downey; Todd Amphitheater, U. H.

Thursday, October 14

- 8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Walter Walker and H. M. Stauffer; M-109, U. H.
- 8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans' Hospital.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans' Hospital.
- 11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.
- 11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hospital.
- 12:00 - 1:00 Physiological Chemistry Seminar; 214 M. H.
- 1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.
- 4:00 - 5:00 Bacteriology and Immunology Seminar; Effect of Low Temperatures on Micro-organism; John Ulrich, Hormel Institute of Austin; 214 M. H.
- 4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.
- 5:00 - 6:00 X-ray Seminar; Dr. Rigler and Staff; Powell Hall Amphitheater,

Friday, October 15

- 8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.
- 9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U. H.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.
- 10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans' Hospital.
- 10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.
- 11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, A. V. Stoesser, and Staffs; Minneapolis General Hospital.
- 11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; the Convulsive Disorders; R. L. Meller and J. A. Resch; Powell Hall Amphitheater.
- 12:00 - 1:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital; Small Class Room.
- 1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.
- 1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.
- 3:00 - 5:00 Kellogg Lecture; Roentgen Diagnosis of Neoplasms of the Stomach and Roentgen Diagnosis of Gall Bladder Disease.

Saturday, October 16

- 7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.
- 8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor West Wing, U. H.
- 9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.
- 9:00 - 9:50 Surgery-Roentgenology Conference; O. H. Wangensteen, L. R. Rigler, H. M. Stauffer, and Staff; Todd Amphitheater, U. H.
- 9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.
- 9:00 - 12:00 Neurology Conference; Station 60, University Hospital.
- 10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

- 10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.
- 11:00 - 11:50 Urology Seminar; Neurogenic Vesicle Dysfunction; John Emmett, Mayo Clinic; E-101, U. H.
- 11:00 - 12:00 Anatomy Seminar; Experimental Evidence of the Production of Adrenotrophin by the Fetal Hypophysis, L. J. Wells; Report of Symposium on the Respiratory Disease Held at Bethesda, Maryland, J. S. Hartman; 226 I. A.

II. CONVULSIVE DISORDERS IN ADULTS

Robert L. Meller
Joseph A. Resch

Introduction

A convulsive disorder is a state produced by an abnormal excessive neuronal discharge within the central nervous system. The clinical manifestations will be as diversified as the functions of the various cells of the nervous system. By the term convulsive disorder is meant epilepsy. It is felt that the new terminology is preferable for two reasons. First, the connotation of epilepsy to the average person is that of a horrible and incurable disease. Second, there is the danger of acceptance on the part of the physician of epilepsy as the diagnosis of a disease entity in itself rather than consideration of it as a symptom of underlying pathology. To our way of thinking, a convulsive disorder implies that we are dealing with a symptom, the cause of which is also to be listed to complete the diagnosis. The old term idiopathic or essential becomes "convulsive disorder due to unknown cause." This is also in conformance with the manual of the nomenclature of diseases used in our hospitals. A criticism of the term convulsive disorder is that not all of the convulsive disorders are characterized by convulsions. We

feel, however, that the advantages of the term outweigh this inaccuracy. Others feel that the way to remove the stigma of the old terminology is enlightenment of the laymen through an educational campaign.

The extent of this disability should be mentioned. About 650,000 people in the United States, roughly 1 in 200, have a convulsive disorder. However, figures cannot adequately express the plight of many of these people, especially the younger ones, who through the ostracism unwittingly imposed by ignorance of the community often lead lives of loneliness and frustration.

Classification of the Convulsive Disorders

It was brought out in the definition of a convulsive disorder that the clinical manifestations would depend on the function of the group of cells which were over-reacting. For the sake of brevity the term "seizure" will be introduced at this time as being synonymous with convulsive disorder. The classification which is about to be given is considered to be the most accurate since it gives a key to the location of the initial neuronal explosion in the pattern of the seizure to which the patient is subject. It is the clinico-anatomical classification of Penfield and Erickson.

CLINICAL TYPE

LOCALIZATION

- | | |
|-----------------------------------|---|
| A. Somatic Motor Seizures | |
| 1. Generalized Seizure | Complete Motor |
| 2. Jacksonian Seizure | (Precentral Gyrus
Postcentral Gyrus) |
| 3. Masticatory Seizure | Postcentral Gyrus |
| 4. Simple Adversive Seizure | Frontal Lobe |
| 5. Tonic Postural Seizure | Brain Stem
(Decerebrate; Opisthotonic) |
| B. Somatic Sensory (Auras) | |
| 1. Somatosensory Seizure | (Pre-Rolandic Gyrus
Post-Rolandic Gyrus) |
| 2. Visual Seizure | Occipital Lobe |
| 3. Auditory Seizure | Temporal Lobe |
| 4. Vertiginous Seizure | Temporal Lobe |
| 5. Olfactory Seizure | Uncinate Lobe |

C. Visceral

1. Autonomic Seizures Diencephalic

D. Psychical

1. Dreamy State Temporal Lobe
2. Forced Thinking Frontal Lobe
3. Stereotyped Behaviour Frontal Lobe
4. Automatism
5. Petit Mal
6. Post-Status Epilepticus Psychotic States

The main features of each of these seizures can be outlined as follows:

A. SOMATIC MOTOR SEIZURES

1. The Generalized Seizure or convulsion may be the end stage of any one of the other types. It is characterized by loss of consciousness, associated with tonic stiffening, and/or clonic jerks of the whole body, added to which there may be evidences of autonomic discharge such as micturition.
2. A Jacksonian Seizure consists of local movements of some part of the body; in a Jacksonian "march" there is spread of the movement from one part of the body to another.
3. Masticatory Seizures are attacks of smacking, salivation, chewing and swallowing usually not remembered by the patient.
4. Simple Adversive Seizure involves a coordinated movement in which there is turning of the head, usually with conjugate deviation of the eyes to which patient is turning. The movement continues until it produces a half turn or even several turns of the body before other phenomena supervene. It usually is associated with unconsciousness but need not be.
5. Tonic Postural Seizure results in rigidity of the trunk with extension of all extremities.

B. SOMATIC SENSORY SEIZURES

1. Somatosensory Seizures are tran-

sient or prolonged sensations of tingling, numbness, sense of movement, desire to move, or very occasionally pain. A detailed march may occur from one somatic part to the next one. It may spread so as to produce motor movement in the same member.

2. Visual Seizures consist of lights, sometimes colored or dimming of vision or blindness.
3. Auditory Seizures are characterized by simple sounds, e.g., buzzing or drumming which are referred by the patient to the opposite ear.
4. Vertiginous Seizures are frequently reported by the patient as dizziness or unsteadiness.
5. Olfactory Seizures are also known as "uncinate fits" because of their localization to uncinate gyrus. Their chief feature is a disagreeable odor.

C. VISCERAL SEIZURES

These seizures may be viscerosensory or visceromotor or a combination of the two. The sensory phenomena may be an epigastric aura, a sense of nausea, or a sense of oppression or fear. Under visceromotor phenomena may be listed pupillary, vascular, gastrointestinal and pilomotor reactions.

D. PSYCHICAL SEIZURES

1. Dreamy State Seizures include illusional or hallucinatory seizures. The illusional seizure is a rather sudden alteration of the patient's perceptions resulting in a sudden

feeling of familiarity with the present situation, or of strangeness, or of being far away. Sometimes only one sense may be involved with sounds being louder or objects being altered in size. The hallucinatory seizure is more complicated and the patient is not aware of his surroundings or only partially so, resembling the dreams that occur in normal sleep.

2. Forced Thinking is an episode during which the same thought or idea repeats itself in an uncontrolled fashion and during which time the patient is out of contact with his environment. On recovery he is frequently able to recall the idea.
3. Stereotyped Behaviour consists of a prolongation of the activity in which the patient was engaged at the onset of seizure. The patient is unconscious during the episode and cannot recall his actions.
4. Petit mal is a term which should be reserved to describe short interruptions of the stream of consciousness. The patient learns of them from evidence of lapse of time. Observers note a vacant expression and perhaps a suspension of productive activity. The term is erroneously used when it is applied to any seizure of short duration.
5. Automatism is the state in which an individual does not have conscious control of activity. If it occurs after a seizure it is called post-ictal automatism. It is felt that there is involvement of the highest levels of integration of the nervous system, allowing the individual to act irresponsibly although in a physically well coordinated manner.
6. Psychotic States are actually post-ictal phenomena usually resulting from severe or repeated seizures over a long period of time. These patients are frequently very violent and often extremely dangerous during the episode.

It will be seen that from the foregoing classification of clinical manifestation that unless the practitioner is aware of some of the nuances of these disorders many cases could escape detection. Undoubtedly, there are considerably more cases of convulsive disorders than the 650,000 known to exist in the United States.

Etiology

Heretofore, too many cases have been relegated to the category of "idiopathic epilepsy" (or in the newer terminology "convulsive disorder due to unknown cause"). This group is a large one because symptoms often appear many years after the initial cerebral injury and therefore no apparent cause is elicited at the onset of the first seizure. A careful history especially in reference to early trauma and infectious diseases, frequently brings out a forgotten source of brain damage. The electroencephalogram comes to our aid on this point. It has been shown rather frequently in our series of cases that the brain waves show a focus of abnormality indicating some previous damage to the underlying brain. Other records show evidence of diffuse cortical damage. At present all our cases are being subjected to a careful Seizure History designed to bring out forgotten or overlooked factors of etiological significance. The study of a patient for a convulsive disorder in the Neurology Clinic, includes the use of various diagnostic procedures designed to aid further in bringing out causes of a patient's seizures. At the present time this work-up includes the Seizure History, a neurological examination, an electroencephalogram, a skull x-ray, fasting blood sugar (and if possible glucose tolerance test), psychometric examination, spinal puncture, and where indicated, a pneumoencephalogram. Table I indicates the results of some of these studies. Penfield and Erickson¹ have correlated the age of onset of seizure with the presumptive cause of the seizures as follows:

<u>AGE OF ONSET</u>		<u>PRESUMPTIVE CAUSE</u>
Infancy	0-2	Birth Injury, Degeneration, Congenital
Childhood	2-10	Birth Injury, Febrile Thrombosis, Trauma, Cryptogenic (Idiopathic)
Adolescence	10-20	Cryptogenic, Trauma
Youth	20-35	Trauma, Neoplasm
Middle Age	35-55	Neoplasm, Trauma, Arteriosclerosis
Senescence	55-70	Arteriosclerosis, Neoplasm

- - - -
Table I

SPECIAL STUDIES ON A GROUP OF
108 PATIENTS WITH CONVULSIVE DISORDERS

	<u>Total Tested</u>	<u>Number Abnormal</u>	<u>Remarks</u>
Skull x-ray	87	16 or 18.4%	Increased intracranial pressure - 3 Changes in dorsum sellae - 3 Bony defect - 2 Internal hydrocephalus - 1 Osteoma in inner table - 1 Hyperostosis of frontal bone - 2 Bilateral calcification of basal nuclei - 1 Bone defect or deformity - 4 Cholesteatoma - 1
E.E.G.	51	35 or 68.6%	Diffuse abnormalities - 28 Focal abnormalities - 7
Blood Sugar	62	0	All within normal limits
Glucose tolerance Test	13	3 or 21.1%	Bizarre curve - 1. Elevated curves - 2
Air Studies	46	13 or 28.3%	Cerebral atrophy - 6 Space-occupying lesions - 4 Distorted ventricles - 2 Enlarged subarachnoid spaces - 1
Spinal Puncture	69	5 or 7.3%	Elevated protein - 2 Positive Wassermann - 1 Elevated colloidal gold curve - 2
Psychometric Examination	68	40 or 57.7%	1. Low I.Q. 2. Abnormal profiles on Minnesota Multiphasic Personality Inventory 3. Evidence of deterioration due to organic brain damage
Psychiatric Consultations	15	15 or 100%	Psychiatric entities of various types

Our data which is now in the process of being analyzed would indicate that the so-called cryptogenic or idiopathic convulsive disorder is relatively uncommon if one considers in detail the patient's early history and evaluates these patients carefully with the various laboratory procedures.

Treatment in the Convulsive Disorder

The average practitioner considers drug therapy as constituting the sole method of attack on the convulsive disorder. This has time and again been proven to be a narrow and often inadequate approach. In reference to our original definition it is found that the convulsive disorder is predicated on an excessive discharge of neurones. This excessive discharge is precipitated by various external and internal factors. Any rational system of therapy will include the elimination of factors which are known to increase the frequency of seizures. Such factors are anxiety, frustration, tension, excessive fatigue, irregular or inadequate meals, excessive hydration and exposure to toxins, e.g., alcohol and carbon monoxide. The emotional reaction of the patient caused by his attitude and that of others toward his illness is probably the most important factor in the precipitation of seizures and is the most difficult to rectify. In addition to the removal of contributing factors above, drug therapy is used for the chemical suppression of the excessive neuronal activity. An adequate therapeutic regime then can be outlined as follows:

1. PSYCHOTHERAPY: In a narrow sense the therapist engages in psychotherapy on an individual basis, depending upon the symptoms requiring alleviation by certain simple and generally applicable techniques, such as reassurance, explanation, ventilation, etc. In a broader sense it means education of the patient and his family. There exists an organization called the American Epilepsy League which was founded in 1939. This organization, which has many local chapters, acts in advisory and educational capacity. It is an organization of laymen designed to

improve the lot of the patient both by his education and that of the general public. The patient should be referred to the local chapter of this organization so that he may benefit by the educational program. As far as we can determine, no such organization exists at the present time in this area. There is a definite need for it. Another psychotherapeutic measure of general nature is the occupation of the patient either in gainful employment or school work. Most of the employed patients have their jobs because the existence of their illness is not known by the employers. Insurance companies do not care to assume the alleged excess risk presented by a patient with convulsive disorder. No legal provision exists in Minnesota, and for that matter in most other states, whereby a patient with convulsive disorder may sign a waiver releasing the insurance carrier of liability in the case of injuries due to his disability. There are actually few work restrictions required. The outstanding of these are the driving of automobiles or similar vehicles and the operation of certain types of machinery. It is felt by at least one clinic that all restrictions should be removed in the case of a patient who has been controlled for a year.

2. DIET: The patient should have his meals at a regular time and they should consist of a well-balanced diet.

3. AVOIDANCE OF EXCESSIVE FATIGUE: This should be accomplished through regular and adequate rest or sleep, and the avoidance of work beyond the individual's physical or intellectual capability.

4. THE AVOIDANCE OF TOXICANTS: The chief offender in this group is alcohol. Abstinence from alcohol beverages is required. There are also industrial poisons, e.g., carbon monoxide in garage work. The patient should not engage in occupations where these are a hazard. The imposition of toxins on neurons which are already functioning improperly is not considered wise.

5. DEHYDRATION: Our procedure is to limit fluids to approximately 1000 cc. per day. The rationale behind this procedure

is based on the concept that an excessively hydrated brain has a lowered threshold for seizures.

6. SURGICAL TREATMENT: Surgical approach in the case of neoplasms and other operable conditions is obvious. In recent years at least two centers have engaged in extirpation of cortical areas considered to be the foci of seizures. This work is done on such a small scale that it is not generally applicable to the management of convulsive disorders. It has been mentioned for the sake of completeness.

7. DRUG THERAPY: This will be discussed in more detail by Dr. Meller at the end of this report.

The Clinic for Convulsive Disorders

In the course of caring for patients with the convulsive disorders in the Neurology Clinic, it was found that they required special care if they were to be properly studied and evaluated, if their emotional and social factors were to be controlled, and if their medication was to be properly regulated. Therefore, some years ago, Dr. A. B. Baker and later Dr. Robert Meller began to set aside a certain portion of their clinic time for the more detailed study and treatment of patients with convulsive disorders. Dr. Fae Tichy followed Dr. Meller and subsequently others of us have had the opportunity to work with these patients. To facilitate matters these patients have been separated from the Neurology Clinic proper and are cared for by the Clinic for Convulsive Disorders which meets at a separate time. There are approximately 120 patients on the active roster of this clinic. They are seen by appointment at intervals varying from weeks to months, depending on the needs of a particular case. Before receiving an appointment to this clinic a patient has already proceeded through the regular channels of the Out-Patient Clinic (including the Neurology Clinic). Once the patient has been assigned to the Clinic for Convulsive Disorders, responsibility for his maintenance is then assumed by that unit. This includes a neurological re-examination, re-

quests for additional laboratory work, requests for consultation from other clinics, correspondence pertaining to the patient, regulation of medication, and the making of appointments. It is interesting to note the University of Colorado Medical Center² has a clinic which functions very much like ours. The advantages of the clinic can be summarized as follows:

1. TEACHING PROGRAM: The Fellow in charge of the clinic receives considerable practical experience in the management of convulsive disorders. The Junior Clerks writing up the Seizure History in the Neurology Clinic proper receive orientation in the salient points of evaluation of a patient with convulsive disorder.

2. THE PATIENT: There is definite benefit gained from the fact that the patient is given attention from nurses, social workers, psychologists and physicians who are definitely interested in his case and who accept him. There are also other patients with him at the clinic who also suffer from convulsive disorder, and he realizes that he is not alone in his problem. The patient has a sense of "belonging". There is, therefore, a certain amount of group psychotherapy in the routine operation of the clinic.

3. CLINICAL RESEARCH: A standard group of patients who have had a rather thorough preliminary study are available for clinical research. As a matter of fact several projects are now under way. Mr. Wentworth Quast, a graduate student in psychology, is at present engaged in performing some psychological studies. Miss Jean Cummins, a social worker, is analyzing a group of selected cases in which the Social Service Department has functioned. Their results when completed will be reported elsewhere. A project which has been completed and from which a great deal has been learned is concerned with the study of the efficacy of various drugs in the control of seizures. This has been conducted largely under the supervision of Dr. Robert Meller who will now give you his report.

Drug Treatment

Before embarking on a discussion of the drug therapy in the convulsive disorders, it is important to re-emphasize what Dr. Resch has already pointed out; namely, that drug therapy is only a part of the total treatment of convulsive disorders. Frequently it is the neglect of this fact that results in dissatisfaction to both the physician and the patient. It cannot be too strongly emphasized that the convulsive disorders cannot be satisfactorily handled simply by supplying the patient with a prescription for some anti-convulsant medication. The regulation and control of the patient's medication is an individual problem. One must not only find the drug or combination of drugs which will give the best results, but one must frequently alter the drug schedule to fit the shifting needs of the patient. For example, many female patients require a different drug routine during the phases of their menstrual cycle, the usual change being an increase of medication at the time of menstruation. Frequent changes are often necessary to compensate for the increased tendency to attacks during periods of increased emotional tension. For example, one of our patients found it necessary to double the amount of his medication whenever he spoke before his sales organization. Many patients notice a greater tendency toward side reactions from their medication when they have colds or other febrile illnesses. Such reactions naturally must be compensated for in the drug routine. This is of particular importance in individuals given large doses of medication - amounts which are just under the threshold of toxicity.

Recognizing these factors in the medicinal treatment of the convulsive disorders, it becomes apparent that an intimate knowledge of the comparative value of each drug in the various types of the convulsive disorders is most essential to a proper handling of these patients. Consequently, the following study was instituted in an attempt to compare the value of the different available anticonvulsives. Each of the drugs was given to the same group of patients. The use of the same patients enabled us to compare the effect of each drug under fairly similar

circumstances. In each patient of this series an attempt was made to obtain the best possible seizure control with one drug before changing to another. Thus, each patient in the series had a trial with each drug until maximum benefits were obtained or until he showed toxic symptoms from the drug.

Before presenting our material, it might be appropriate to mention the anti-convulsive drugs now available, their method of administration, and the possible toxic effects from overdosage. No mention can be made of routine dosage since there is no standard dose of any of the drugs used in this condition. The actual dosage can be defined only as that amount of drug which is necessary to produce the best control effect without or with a minimum of undesirable toxic symptoms.

1. Bromides: Bromides were some of the first drugs used in the control of convulsive disorders. Bromides were introduced by Sir Charles Locock in 1853.³ Although bromides have been replaced by newer medications (chiefly barbiturates and hydantoins), they are still useful in many individuals. Many obstinate cases may be brought under control with a proper combination of bromides and barbiturates. The common toxic effects of bromides are skin reactions and drowsiness. Long continued use may result in the development of a toxic psychosis.

2. Phenobarbital: Phenobarbital was introduced by Hauptmann⁴ in 1912. This drug soon became and continued to be the treatment of choice until very recently. The common side effects are drowsiness, skin reactions, and gastro-intestinal disturbances. Drowsiness is by far the most common and disturbing reaction.

3. Mebaral: Mebaral, a Winthrop preparation of mephobarbital, is supplied in grain 1/2, grains 1 1/2, and grains 3 tablets. In our clinic we have found that this drug produces a minimum of undesirable reactions, even in large doses. The side reactions, when they occur, are similar to those of phenobarbital.

4. Dilantin: Diphenylhydantoin

sodium was introduced by Putnam and Merritt⁵ in 1937. Dilantin is supplied by Parke Davis and Company in grain 1/2 and grains 1 1/2 capsules. The side effects are tremor, dizziness, restlessness, ataxia, skin reactions, gastro-intestinal symptoms, and hypertrophy of the gums. Many patients can take dilantin for many years without untoward symptoms and then rather rapidly develop a severe ataxia which subsides when dilantin is withdrawn.

5. Mesantoin: 3-methyl 5, 5 phenyl-ethyl-hydantoin was first reported by Loscalzo⁶ and Kozol⁷ in 1945 and 1946. Mesantoin is a Sandoz product supplied in grain 1 1/2 tablets. Its side reaction resembles those of dilantin and consist of tremor, dizziness, drowsiness, ataxia, skin reactions, gastro-intestinal symptoms, blood dyscrasias, and a curious manifestation which resembles a febrile illness with adenopathy. In cases where drowsiness is the predominant symptom, it can frequently be relieved by the administration of dexidine sulfate.

The above mentioned drugs are all useful for the control of major motor seizures and, with the exception of mebaral, are of little value in the control of minor seizures. For the control of the latter, in addition to mebaral, one can use the following:

6. Tridione: 3, 5, 5, trimethyl-oxazolidine - 2, 4-dione was introduced by Lennox⁸ in 1945. It is an Abbott product supplied in 4 1/2 grain capsules. Its most characteristic toxic symptoms consist of photophobia, skin reactions, and gastro-intestinal symptoms. A rare and disturbing toxic effect is the development of an aplastic anemia. For this reason repeated blood studies at least every two weeks are indicated in any patient placed on this drug. It must also be kept in mind that occasionally tridione will precipitate grand mal seizures even though the minor seizures are controlled. For this reason one of the drugs controlling major seizures must always be given with the tridione.

7. Glutamic acid: Glutamic acid has been used in the control of minor seizures⁹ but since large doses of medicine

are necessary and since its action is unsustained, the therapeutic value of this drug is of doubtful worth.¹⁰

It is a well known fact that different combinations of the above mentioned drugs are frequently much more effective than any single drug.

The results of our investigations with drug therapy have been summarized in Tables II, III and IV.

Table II summarizes the results of our drug therapy in the total number of 108 patients treated up to the present time. Many of these patients have been placed upon different combinations of the drugs. As will be seen from the Table, by far the most favorable results were obtained from the use of Phenobarbital and Mebaral. In each of these drugs approximately 75% of the patients were controlled or definitely improved. However, in this group of patients, the Phenobarbital produced a much higher percentage of toxic symptoms than did the Mebaral. It is for this reason we have preferred the use of Mebaral in our Clinic. From our experience we have been impressed by the results that can be obtained by the combined use of the anti-convulsives. By the addition, for example, of Mebaral and Dilantin, one can obtain 85% control or improvement in patients with convulsive disorders. The one weakness with this entire Table is the fact that many more patients were treated with Phenobarbital and Mebaral than with the hydantoins. This discrepancy in the number of patients treated by the individual drugs tends to make a specific comparison of these medications somewhat questionable. An attempt has been made to correct this weakness in Table III where the individual drugs have been given to the same patients and where a specific comparison is possible.

Table III is a comparison of the four most commonly used drugs in the convulsive disorders when given to the same group of patients over a period of years. Obviously when the different drugs were tried with the same group of patients, one has the most ideal conditions in which to evaluate their efficiency. The greatest difficulty in setting up such a

Table II

SUMMARY OF RESULTS WITH DRUG THERAPY

	Total No. Points	Controlled	Improved	Not Controlled	Toxic Symptoms	Controlled or Improved
Phenobarbital	65	34 or 52.3%	17 or 26%	14 or 21.5%	15 or 23%	51 or 78.3%
Mebaral	71	38 or 53.5%	16 or 22.5%	17 or 24%	5 or 7%	54 or 76%
Dilantin	42	16 or 39%	9 or 21.4%	17 or 40.5%	11 or 26.2%	25 or 60.4%
Mesantoin	25	11 or 44%	5 or 20%	9 or 36%	9 or 36%	16 or 64%
Phenobarbital and Mesantoin	1			1	1	
Phenobarbital and Dilantin	11	5 or 45.4%	2 or 18%	4 or 36.3%	3 or 27.2%	7 or 63.4%
Mebaral and Mesantoin	12	4 or 33.3%	4 or 33.3%	4 or 33%	2 or 16.6%	8 or 66.6%
Mebaral and Dilantin	28	15 or 53.6%	9 or 32%	4 or 14.2%	4 or 14.2%	24 or 85.6%
Total number of instances in which drug therapy was used	255	123 or 48.2%	62 or 24.3%	70 or 27.4%	50 or 19.6%	185 or 72.5%

Table III

COMPARATIVE RESULTS ON 25 PATIENTS

	Controlled	Toxic or Not Controlled
Phenobarbital	6	19
Mebaral	16	9
Dilantin	7	18
Mesantoin	15	10

Table IV

TOXIC REACTIONS IN DRUG THERAPY

	Drowsi- ness	Gum Hyper- trophy	Lymph- adenopathy	Rash	Tremor	Ataxia	Totals
Phenobarbital	19						19
Mebaral	7			2			9
Dilantin	1	2		1	8	6	18
Mesantoin	1		1	3	2	3	10

controlled experiment, however, is the fact that it is almost impossible to follow a large series of such patients over the number of years required for an adequate evaluation of a series of drugs. To date we have been able to follow through such a study on 25 patients (Table III). As will be seen from this study, the best results were obtained from Mebaral and Mesantoin, and in view of the relative ease with which Mebaral can be administered to most patients, it would appear that this drug at the present time is one of the best for the treatment of the convulsive disorders in general.

Finally, Table IV is a listing of the relative frequency of the different types of toxic symptoms resulting from the anti-convulsive medication used in our test group of 25 patients. By far the most frequent toxic symptom was lethargy or drowsiness which was produced predominantly by both Phenobarbital and Mesantoin. Aside from the drowsiness the majority of the toxic symptoms resulted from the use of the hydantoins (Mebaral and Dilantin) and consisted of tremor, ataxia, and a severe skin rash. The ataxia may be of such intensity as to completely incapacitate the patient. The rash may be so severe as to require hospitalization for a long period of time. One of the peculiarities of this hydantoin toxicity is the fact that these symptoms tend to regress very slowly and may be distressing to the patient for a long period of time.

In summary one must emphasize the fact that the treatment of the convulsive disorders is an individual problem in which the drugs play only a limited part. From our own experience with this treatment in

a special clinic devoted to this illness, we feel certain that the great majority of patients suffering from major seizures can be controlled completely on a well regulated regime supplemented by adequate medicinal therapy.

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III. MEDICAL SCHOOL NEWS

Minnesota Medical Foundation

General Medical Faculty Meeting

The annual meeting of the General Medical Faculty will be held on Monday evening, October 11, at 8:00 p.m. in the Auditorium of the Museum of Natural History. Congressman Dr. Walter H. Judd will be the guest speaker. The program will include a discussion of the revised medical curriculum, a brief presentation of other significant developments which have occurred in the Medical School during the past year, and an outline of the plans of the Medical School for the years ahead. New faculty members will be introduced. All members of the faculty are invited. Fellows in the Medical School are especially welcome.

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Streptomycin Conference

The Committee on Streptomycin of the Veterans Administration announces the sixth Streptomycin Conference. This conference will be held October 21-24 in the Assembly Room of the Ramsey County Medical Society, Lowry Medical Arts Building, St. Paul. All Medical School and University Hospital staff members are welcome.

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The present number of the Bulletin will be distributed to the entire membership of the Minnesota State Medical Association in an effort to create greater interest in the Minnesota Medical Foundation and in this Bulletin which is the official publication of that organization and the University of Minnesota Hospitals. The Foundation was organized in 1939 by the Minnesota Medical Alumni Association. The purposes of the Foundation are:

"To promote the welfare of the community by the cooperation of alumni and friends of the Medical School of the University of Minnesota in improving the undergraduate, graduate, and research functions of that institution; to establish scholarships, lectureships, professorships, research and student loan funds in that institution; to publish and promote the publication of a representative medical Bulletin; and in general, by all legitimate and usual means, to advance the interests of the University of Minnesota Medical School and its alumni without consideration for benefits bestowed."

All members of the Foundation receive the Bulletin. All who are interested in furthering the objectives of the Foundation are cordially invited to join.

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Kellogg Foundation Lectures

The following lectures will be given during the week October 11 through October 16. All medical students, interns, and physicians are cordially invited to attend these lectures. A special invitation is extended to University fellows.

Dr. Malcolm M. Hargraves	The Anemias -- Their Diagnosis and Treatment	Mon., Oct. 11, 1948 3:00 p.m., Chapel, Center for Continuation Study.
Dr. Hal Downey	Hemopoiesis	Wed., Oct. 13, 1948 1:00 p.m., Todd Amph.
Dr. B. R. Kirklin	Roentgen Diagnosis of Neoplasms of the Stomach and Roentgen Diagnosis of Gall Bladder Disease	Fri., Oct. 15, 1948 3:00 p.m., Chapel, Center for Continuation Study.