ANTICONVULSANTS : A REVIEW

By

M. L. GUJRAL, K. N. SAREEN AND B. N. DHAWAN

From the Department of Pharmacology, K. G. Medical College, Lucknow University

(Received January 10, 1957)

HISTORICAL

Convulsions are mentioned in ancient books like the Smith Papyrus (1700 B. C.) and Codus Hammurabi (about 800 B. C.). A classic account is given by Hippocrates, "The patient looses his speech and chokes, and foam issues by the mouth, the teeth are fixed, the hands are contracted, the eyes distorted, he becomes insensible, and in some cases the bowels are evacuated". (Hippocrates, Vol. 2). The description is so good that for centuries very little was added to the description of grand mal seizure although it was studied in the days of Renaissance by Paracelsus, who suggested chemical anticonvulsant remedies.

Among the remedies of antiquity one finds a dreadful conglomeration of medicines used for 'St. Valentines disease', "including horse's blood, ashes of ass's hoofs, ears and warm blood of a gladiator and the blood of animals recently slaughtered" (Salter, 1953). Some of the ancient treatments, however, have proved to be of some value. Hippocrates wrote, "patients suffering from the great disease (epilepsy) not affected by quartan fever, if they become affected by it, are freed from epilepsy" (Epid VI, Sect. VI. 5) and "persons attacked with quartans are not readily attacked by convulsions" (Aphos V, 70). Terry (1939) has concluded that in some cases of epilepsy favourable results can actually be obtained by pyrexia induced by plasmodia, sulphur, typhoid, etc.

Epilepsy was regarded throughout the middle ages as a manifestation of the presence of an evil spirit in the afflicted individual. The best way of treatment suggested was to exercise the evil spirit and thereby to urge it to abandon the body during convulsions. The difficulties of treatment were well known in early 19th century when Esquinol put 3 patients in the hospital and tried one treatment after the other on each patient. Each treatment was effective for a short time but none brought a lasting cure (Tempkin, 1945).

The modern era of treatment began in 1857 when Locock introduced bromides in catamennial seizures under the impression that this medication was an anaphrodisiac and therefore might be useful if epilepsy were caused by onanism. Of fourteen cases Locock got good results in thirteen, a therapeutic triumph which no one has achieved since then (Sieverking, 1857; Wilks, 1859). The clinical use of bromides became very popular within a short span of time (Gowers, 1881) and introduced an era in which the greatest stress was laid on the use of sedative drugs (Spratting, 1904). The outstanding achievement of this era was the introduction of phenobarbitone by Hauptman in 1912. He showed it to be superior to bromides in the treatment of grand mal and the lead was taken up by Dercum (1919) and

Grinker (1920). In combination with ketosis of starvation proposed by Geylin (1921) and ketogenic diet proposed by Wilder (1921) it afforded a moderately satisfactory therapy. The main limitation upon its use was its sedative property. Among other barbiturates mention may be made of introduction of Mebaral by Heyde and Blum in 1932.

In U.S.A., where epilepsy had been no mean sociological and economic problem national experimental research work was started for new antiepileptic drugs without sedative properties and Putnam and Merritt after careful laboratory studies of a large number of substances introduced diphenylhydantoin in 1937. The drug continues to be one of the most effective remedies for grand mal type of seizures. Other hydantoin derivatives soon followed in the wake of success of diphenylhydantoin.

In a systematic search for new analgesic drugs, Spielman in 1944 synthesized many derivatives of oxazolidine-2,4,-dione. In studying the analgesic properties of these drugs, Richards and Everett showed that they have anticonvulsant properties also. Tridione saw the light of the day as a result of their investigations and soon became an accepted drug for the treatment of petit mal triad, which had been refractory to other methods of therapy (Lennox, 1947).

Since then a very large number of synthetic anticonvulsants have been developed and many of them are being evaluated in the clinic. Some of the outstanding developments to merit mention include Phenurone (Everett, 1948), Milontin (Chen et. al., 1951), Atrolactamide (Jenney et al., 1952), Mysoline (Bogue and Carrington; 1953; Goodman et al., 1953) and Hibicon (Harned et al., 1953). Therapy is still by no means perfect but the number of cases that cannot be controlled satisfactorily is rapidly dwindling, and thousands of individuals who would have been otherwise economically dependent are able to carry on a reasonable day's work.

No less important than the development of drugs has been the development of diagnostic methods and study of electrical patterns etc. The elusiveness of diagnosis already plagued the ancient Romans, who were prompted to use tests by which attacks could be provoked artificially in slaves who were on sale (Bercel, 1952). Modern investigations began with Hughling Jackson's study of convulsions and publication of his neurological analysis in 1863. In 1929 Hans Berger presented to the world a revolutionary new method for the investigation of the function of brain in health and disease, namely electroencephalography. The biochemical and neurochemical approaches to the problem are still more recent. The studies of effects of pH changes, inhalation of CO_2, water and electrolytic variations, role of endocrines etc., have all contributed to our knowledge of convulsive disorders (Freedman et al., 1948). All these developments have been very helpful and have given impetus for further work but one is inclined to agree with Bercels (1952), "even though tremendons amount of progress has been made during the last 80 years, it seems that every new diagnostic test and every new diagnostic design has added as many problems as it has solved".

MECHANISM OF CONVULSIVE SEIZURES

An understanding of the nature of convulsive discharge is a prerequisite to any consideration of mechanism of action of anticonvulsant drugs. Several decades ago John Hughlings Jackson, the father of modern concepts of epilepsy, proposed on the basis of his clinical inquiries into aura, onset and pattern of seizures, postictal recovery of function and associated interseizure signs of neurological lesions that the disorder was due to "occasional, sudden, excessive, rapid and local discharges of grey matter." The occurence of post-seizure depression of functions also gave support to the idea of excessive discharge during a seizure. In the many intervening years little has been added to his concepts except the electrical proof of the correctness of his postulates.

In view of the ease with which experimental seizure can be initiated in normal brain tissue by electrical and chemical methods, some mechanism must exist to prevent neuronal activity from producing cerebral explosions. The process of inhibition first proposed by Bubnoff and Heidenhaen (1881) provides such a mechanism. They say that inhibition and excitation are produced in equal amounts by stimulation of grey matter; that inhibition restricts the spread and duration of excitation and that seizures can result when the ratio of excitation to inhibition exceeds unity. Sherrington (1906) has proposed that inhibition can be transformed into excitation by convulsant drugs or by excessive stimulation. Brooks-Eccles hypothesis that the short cells ordinarily inhibiting passively can excite actively if they are made to transmit impulses provides an anatomical basis for Sherrington's view. Brain excitability is further regulated by gross inhibitory areas in the cerebrum operating upon cortex through extracortical mechanisms (Dusser de Barenne and McCulloch, 1939; McCulloch, 1947) and probably by an intracortical mechanism of inhibition also.

Introduction of electroencephalography by Berger has provided direct evidence for Jackson's postulates that abrupt and excessive local discharges are characteristic of seizures. Adrian and Moruzzi (1939) working on single neurones of the pyramidal tract have shown that in order to cause seizures, electrical or chemical stimulation must elicit repetitive discharges of high frequency thus further substantiating Jackson's concept of convulsions.

The nature of the seizure focus is far from clear. The most commonly accepted view is that it consists of a collection of pathological neurones discharging excessively even under normal condition of stress. However as Goodman et al. (1949), point out, the focus may represent normal neurones forced to fire excessively because of abnormal stress, e.g., restricted vascular supply. Vascular abnormalities are often demonstrable at the junction of normal brain tissues and areas of scarring. According to Penfield and his co-workers (1941, 1940) seizures are the end result of progressive neural injury produced by vascular spasm. In some cases prior injury may have destroyed the smallest and most vulnerable neurones of a portion of a nerve

net and thus produced a stable hyperactive focus devoid of its internal inhibitory mechanism. This view obviates the need for involving abnormal stress as a cause of seizures and is consistent with the fact that in many patients seizures continue to occur for years without evidence of progressive neurological change (Goodman et al., 1949). But the brain lesions may exist without producing convulsions and the seizures are intermittent whereas lesions producing them are constantly present. To explain this considerable attention has been paid to physiological precipitating factors which may affect the behaviour of an epileptogenic focus. The important ones amongst these factors are: changes in the pH, pressure of blood gases, blood sugar level, total osmotic pressure and electrolyte composition of fluid environment of brain cells; changes in body temperature; endocrine disturbances particularly of adrenal cortical steroids and post pituitary antidiuretic hormone; and nutritional factors especially effects of starvation, ketosis, pyridoxine deficiency, glutamic acid and exogenous chemical dietary substances (agenised flour) etc. Thus many contributory factors may interplay to influence the brain, predisposed by acquired injury or inherited defect, to produce a seizure.

MECHANISM OF ACTION OF ANTICONVULSANT DRUGS.

Theoretically, the concievable mechanisms by which anticonvulsant drugs might prevent, abort, modify, or reduce the frequency of clinical seizures can be included in 3 broad categories: (a) action on non-neural lesions, (b) action upon the abnormally altered neurones to prevent their excessive discharge; and (c) action upon normal neurones to prevent their detonation by excessive discharge (Toman and Taylor, 1952; Goodman and Gilman, 1955).

The first group includes possible action of drugs in reducing the sensitivity of the abnormal vascular supply of an epileptogenic focus; for example, atropine and antihistaminics have been tried clinically in epilepsy (Goodman et al., 1949). The possibility of drugs acting via vascular action assumes greater significance in view of Penfield's work (1940, 1941) regarding the role of these vessels in precipitating seizures (vide supra). On this basis a variety of autonomic blocking and stimulating drugs which affect the blood vessels can have an anticonvulsant action. Some of them have been studied by Tainter and his co-workers (1943). According to Aird (1939, 1944) the anticonvulsant action of certain dyes and DOCA also involves stabilization in permeability of cerebral vessels—a mechanism quite different from that of other drugs acting on blood vessels.

The second category of action assumes that anticonvulsants can selectively influence hyperactive neurones without significantly altering the function of normal brain cells. No definite examples of such a differentiation have yet been presented although the ability of diphenylhydantoin to prevent abnormal susceptibility to electroshock seizures in hydrated animals (Swinyard et al., 1946) or the ability of many other anticonvulsants to prevent seizures induced by metrazol, picrotoxin etc., may be cited in favour of this assumption (Toman and Goodman, 1948). But, in general, agents which modify abnormal

excitability or activity of neurones can also be shown to have an effect on normal neurones.

The third and the most important mechanism is the ability of antiepileptic drugs to prevent the spread of convulsive activity from a seizure focus to normal neurones. This may be accomplished either by raising the threshold of normal brain cell to an exciting agent or by decreasing the responsiveness of the excited system. The former group has received by far the most attention. After the laboratory studies of Merritt and Putnam (1937, 1938) a widely held view is that the main action of anticonvulsant drugs is to increase the threshold for seizures. The concept is implicit in the procedures of most of the investigators who have assayed new anticonvulsants and have demonstrated that most of them can raise the threshold either for chemical or electrical stimulation or for both (Alles et al., 1947; Barany and Stein Jensen, 1946; Chen et al., 1948; Everett, 1946; Gibbs et al., 1948; Goodman and Lih, 1941; Keller and Fulton, 1931; Knoefel and Lehman, 1942; Merrit et al., 1945; Swinyard and Goodman, 1946; and others). The Utah group of workers (Goodman et al., 1946; Toman and Goodman, 1947; Toman et al., 1946; 1947), however, do not entirely agree with this view. They have shown for example that diphenylhydantoin does not raise the threshold either for metrazol seizures or for minimal electroshock seizures.

Less attention has been paid, however, to the effect of drug action upon ability of the brain to respond. Toman et al. (1946), have shown that modification of the ability of the brain to respond to seizure stimuli is a common property of most of the clinically accepted anticonvulsants. This is also evident in the abolition of the extensor tonic phase of supramaximal shock seizures. Barany and Stein Jensen (1946, 1947) also have found that the common anticonvulsants shorten the tonic phase of experimental seizures. Barany (1947) as a result of his exhaustive studies has suggested that a small degree of synaptic depression is produced by anticonvulsant drugs. This has little importance upon small reflex chains but the same effect at each synapse in a reverberating long chain system supposedly involved in the spread and maintenance of convulsive activity is amplified in accordance with the total number of synaptic links in the circuit. This might make impossible the initiation, spread and maintenance of a seizure. An ancillary concept is that small rises in threshold may cause previously excitatory links to become inhibitory (Sherington, 1906) in accordance with the Brooks-Eccles theory of inhibition.

Depending upon the effects of anticonvulsant drugs on properties of individual neurones, Goodman and Toman (1948) have constructed a hypothetical schematisation. They say that alterations in dynamic (temporal) properties of the nerve—such as increased rate and extent of accommodation, decreased autorhythmicity, and increased recovery time through suppression of supernormal phase or prolongation of subnormal phase—may prevent local spread of discharges or initiation of seconday seizure foci in distant centres by the primary focus. According to them drugs acting in this manner

primarily benefit grand mal, motor or sensory Jacksonian seizures and psychic seizures. Similarly alterations in static (non temporal) properties of the nerve—such as increase in threshold or in membrane resistance, and decrease in action potential, in amplitude or in quantity of excitatory substance may supress focal seizure discharges or nonconvulsive driving of distant centres by a primary focus. Drugs acting in this manner should find particular application in pykno-epilepsy, akinetic seizures and myoclonus.

Drugs like amphetamine, which excite rather than depress the central nervous system, cannot, however, act by any one of the above methods and the same is probably true of glutamic acid. In as much as sensory stimulation may occasionally abort cortical seizures (Jackson, 1931; Penfield and Erickson, 1941) and because seizure discharges are more common in sleep than during the waking state (Gibbs and Gibbs, 1947) it is probable that a drug induced increase in the activity of brain may inhibit discharges from the seizure foci (Goodman et al., 1949). Their exact mechanism of action, however, is unknown.

Some light on the mode of action of anticonvulsants is also thrown by a study of their action on E. E. G. There are two general types of actions of anticonvulsants on E. E. G. On the one hand there are effects upon the normal E. E. G., which may be characteristic of the wide actions of the drug and are more specific for the drug than for the anticonvulsant action. On the other hand there are effects upon the abnormal E. E. G. associated with convulsive disorders, manifested as complete supression of the dysrhythmia or its modification by shortening it, slowing of the frequency and disintegration of the rhythm of discharge, change in abnormal wave form etc. Toman and Davis (1949) believe that the modus operandi of these drugs involves the stabilisation of neuronal threshold against excessive stimulation or exciting agents so as to prevent excessive facilitation and discharge of impulses at high frequency.

SCREENING METHODS FOR NEW ANTICONVULSANTS

A. LABORATORY ASSAY.

The introduction of experimental methods in the evaluation of antiepileptic drugs has accelerated the search for better drugs and has radically changed the outlook of epileptics with the result that today the symptoms of majority of the patients can be satisfactorily controlled.

Upto the present time there is no single laboratory test which can definitely demonstrate the presence or absence of anticonvulsant activity of a drug and thus adequately screen potentially useful antiepileptic agents. Hence it is imperative to integrate the most effective techniques known at present into a comprehensive routine assay procedure composed of a battery of assay tests for rapidly screening and differentiating large series of new drugs (Swinyard, 1949).

It is now generally agreed that rat and mice are the most suitable laboratory animals for producing various types of seizures (Sampson and Fernandez, 1939; Toman et al., 1949; Goodman et al., 1946). In the succeeding pages the various test details that are given are for these animals,unless otherwise mentioned.

Both acute and chronic methods are available for initiation of experimental seizures. The majority of acute methods utilise either electrical or chemical measures for inducing seizures while chronic epileptogenic foci are employed for production of chronic seizures.

Electrical Methods.

Albertoni (1882) is accredited to be the first person to employ Faradic stimulation of cortex through trephined skull. A similar procedure has also been used by Bikeles and Sbyszewski (1914). The use of electrically induced convulsive responses in the study of anticonvulsant drugs has become popular, however, since the pioneer work of Putnam and Merritt (1937) and the introduction of electroshock as a therapeutic procedure in psychiatry by Cerletti and Bin (1938). The numerous electrical methods of producing seizures can be grouped under four heads:

1. Minimal Electroshock Threshold Tests, 2. Hydration Electroshock Seizure Tests, 3. Maximal Seizure Pattern Tests, 4. Psychomotor Seizure Tests.

1. Minimal Electroshock Threshold Tests.

Jellinke (1920) and Schilf (1922) are the first investigators who have measured seizure threshold for alternating current applied for 0.5 seconds through corneal electrodes. Speigel (1937) has determined convulsive reactivity of cats and rabbits by electrical stimulation through the eye balls with an apparatus which permits variations of both voltage and duration of an alternating current. He expresses the threshold as ampere seconds.

Putnam and Merritt (1942), Merritt et al. (1938), Knoefel and Lehman (1942), Tainter et al., (1943); and Merritt et al. (1945), have used buccal and occipital electrodes and have determined the convulsant threshold in terms of current strength with a constant duration of current flow. Cats between 2-4 kgm. having threshold of 15-25 m.a. when current is passed for 10 seconds are taken, and 2 hours after the administration of the drug the rise of threshold is measured. A rest of 5 minutes is allowed between two ineffective shocks. The current amperage is gradually raised only upto a maximum of 50 m.a. to conserve animals (Merritt et al., 1945 b).

Tainter et al. (1943) and Chu et al. (1948) have employed rats, rabbits and cats. Stimulation in rats begins with a current of 6 m.a., in rabbits with 14 m.a. and in cats with 20 m.a. It is repeated at 5 minute intervals and the current is increased by 2 m.a. each time until threshold value is reached.

Kozelka et al. (1942) and Alles et al. (1947) on the other hand have determined the convulsive threshold in terms of duration of current flow. They have produced convulsive seizures in rabbits by passing a 50 m.a. 60 cycle/sec. current through the head of the animal by means of 3/4" square copper electrodes held in position on temporal region with elastic tapes.

Barany and Stein Jensen (1946) have passed alternating current through electrodes placed in the external auditory meatus and determined the effects of drugs on seizure threshold for both long and short periods of stimulation.

Lanphier (1949b) has suggested the use of buccal electrodes in hamsters and this has proved a very useful assay procedure in the hands of Orcult and Prytherch (1956). A pair of symmetrical electrodes, made by fastening loops of 10 gauge copper wire at the end of insulated, rigid steel rods mounted on a stationary base, are shaped to fit comfortably inside the buccal pouches of a hamster. Shock is induced by an A.C. current of 60 cycles/sec. and approximately 110 volts. With 10.0 kilo-ohms resistance in the circuit, the electrodes are applied, the dial is set at 20 and the current is switched on. Every 5 seconds, the current is increased by 5 units until a maximal tonic convulsion is observed. This is a characteristic and distinct end point involving flexion of the forelimbs and abduction quickly followed in rapid succession by flexion and extension of hind limbs, the last state being maintained in a board like rigidity for several seconds. The current is switched off immediately after the convulsion or at a dial reading of 75 whichever is attained earlier.

A somewhat similar method has been employed in rats by Everett and Richards (1944). They induce convulsions by using a special helmet electrode fixed rigidly to shaved head and a second electrode held firmly to the roof of the mouth by a jaw clamp. Changes in threshold by the drug are measured in terms of voltage. The normal convulsive threshold is first determined by gradual increase in the voltage until convulsions appear which persist 5-15 seconds after cessation of the current. The period of stimulation is 10 seconds with 5-10 minute intervals between subsequent stimuli.

A slightly different technique has been adopted by the Utah group of workers (Toman et al., 1946; Goodman et al., 1953; Swinyard et al., 1953 and others). The test, designated the Minimal Electroshock Seizure Threshold Test (M. E. T.), is performed in rats and mice and it measures the ability of anticonvulsants to raise by 20 percent the alternating current necessary to evoke a minimal clonic seizure. These workers use Spiegel corneal electrodes and deliver 60 cycle alternating current of varying strength but independent of the external resistance for 0.2 seconds. An initial control determination of threshold for minimal electroshock seizure is made in each rat or mice. Shocks are given at 6-8 hours, with small (3 percent) increments or decrements in current intensity unless a minimal seizure occurs. A minimal seizure in rat is defined by them as consisting of ten or more seconds of facial clonus without loss of righting reflex. With this criterion the threshold

varies between 26-36 m.a. and a change of 5 percent in threshold can be easily detected. In mice the strength of the current varies between 6-9 m.a., depending upon the weight of the animal ; and the threshold seizure (Brown et al. 1953) consists of at least 7 seconds of facial, lower jaw or forelimb clonus, without loss of upright posture. The threshold test is performed every 48 hours until the threshold is established and does not vary by more than 3 percent (0.25 m.a.) in 3 successive determinations. For any one animal the threshold is constant. It, however, varies with age, nutritional state, environmental and body temperature etc. (Davenport and Davenport, 1948; Swinyard and Toman, 1948). Toman et al. (1946) have similarly determined the seizure threshold in rabbits, the end point being the same, i.e., ten or more seconds of facial clonus without loss of righting reflex.

Harned et al. (1953) have used a modification of Putnam-Merritt test (vide supra) in rats, involving stimulation through electrodes attached to ears. The number of m.a. required to maintain the tonic convulsion after a current applied for 10 seconds is noted. A shock of 5 m.a. is given at first and if it proves ineffective 1 m.a. increment at five minutes interval is continued until the threshold is reached. The threshold is again determined after the drug. The rats whose threshold is more than 10 m.a. are not included in the study.

2. Hydration Electroshock Threshold Test (Hyponatremic Electroshock Seizure Threshold Test; H.E.T.—Swinyard et al. 1946; Swinyard et al. 1952; Goodman et al., 1953). Swinyard et al., (1946) find that hydration of an animal artificially lowers seizure threshold and thus enhances its susceptibility to seizures. Darrow and Yavnet (1935) have found that hydration markedly lowers extracellular sodium concentration. Swinyard et al., (1955) have concluded that hyponatremia is the real factor in lowering the threshold and not hydration per se. Under a variety of experimental conditions alterations in brain sodium ratio (i. e., ratio of extracellular to intracellular brain sodium) are correlated with changes in brain excitability (Woodbury, 1952 ; Timiras et el., 1954 ; Swinyard. 1909 b). Most of the observed alterations in the distribution of other electrolytes and water are not closely correlated with the changes in convulsive threshold.

The test is performed in both rats and mice. The minimal electroshock seizure threshold is determined (vide supra) and 10 ml. of freshly prepared isomolar (5.5 percent) glucose solution per 100 gm. body weight is then injected intraperitoneally. The hyponatremic state and concommitant hypersusceptibility to seizures reaches a peak after 2 hours in mice and 4 hours in rats. The degree of reduction on minimal electroshock seizure threshold is 44 ± 1.26 percent of its initial value (Swinyard et al., 1946) in both rats and mice. The drug to be tested is administered at such a time that its peak effect coincides with peak hyponatremia. A single test shock is then given having a current intensity 66 percent of the normal electroshock seizure threshold for each animal. This represents a 50 percent increase above the experimentally lowered hydration threshold and absence of even a minimal seizure is taken as the end point.

3. Maximal Seizure Pattern Tests.

(Toman et al., 1946; Swinyard, 1949; Goodman et al., 1949; Swinyard et al., 1952; Toman et al., 1952; Goodman et al., 1953 and others). Seizures have been produced by this method in rabbits, cats, rats and mice. The maximal seizure consists of "a short flexor and a long extensor tonic component with little or no terminal clonus" (Toman et al., 1946). The following components of the seizure are relatively invariable in character hand sequence : (a) latent period; (b) flexor component of tonic phase; (c) extensor component of tonic phase, followed by abrupt relaxation; (d) clonic phase (frequently absent); (e) period of postictal depression characterised by inability to exhibit contact placing reactions and to maintain a second maximal shock.

Tedeschi et al. (1956) have studied the effects of variations in stimulus intensity on maximal electroshock seizure pattern and duration, and time for 50 percent animals to recover the ability to exhibit a second tonic clonic seizure (RT50) in mice. They find that mean duration of hindlimb tonic flexion increases as stimulus intensity is increased. Mean duration of hindlimb extension is significantly longer only in seizures evoked by a stimulus 800 percent of standard stimulus. The flexion extension ratio progressively decreases as stimulus intensity is increased. Mean duration of terminal clonus does not vary with the intensity of the stimulus. They have also found statistically significant increase in RT50 as the intensity of the stimulus employed to evoke the initial seizure is increased. Some of these findings are not in conformity with the findings of Toman et al. (1946) and this aspect of the problem deserves further study.

Toman et al. (1946) have produced supramaximal shocks in rats with a current of 150 m.a. and 0.2 seconds duration. The average duration of the seizure is 14 seconds. Toman et al. (1952) have also induced supramaximal seizures with a current of 100 m.a. having a pulse frequency of 100 per second, a pulse width of 1 millisecond and duration of 0·33 seconds delivered via corneal electrodes. Harned et al. (1952) have delivered 60 cycles alternating current of 150 m.a. through corneal electrode for 0·3 seconds. Abolition of the extensor component after drug treatment is taken as the end point. (Barany and Stein-Jernon, 1946; Goodman et al., 1946; Toman et al., 1946; Toman and Goodman, 1946).

Bogue and Carrington (1953) have induced maximal seizures in rats by modification of the technique of Kozelka et al. (1942) and Alles et al. (1947) by varying the time rather than the current. Seizures are induced by passing a 7·5 m.a. 50 cycle sinusoidal waveform current by means of padded ear clips. The maximum duration of shock does not exceed 10 seconds. Within a period of 27 seconds a normal rat exhibits the characteristic tonic extension of hindlegs, and the time is recorded. The initial threshold of each animal serves as control. Only those animals who exhibit the tonic extensor component after a shock intensity of 23-24 m.a. seconds are selected for the assay. The maximum shock intensity delivered to a protected animal is 75 m.a. sec.

Anticonvulsant activity is assessed in terms of the dose required to abolish the tonic extensor component of the seizure at this maximal intensity.

Swinyard et al. (1952) and Goodman et al. (1953a) have induced maximal seizures in mice by a current of 50 m.a. delivered for 0·2 seconds by means of corneal electrodes. The mice frequently die of anoxia at the end of the tonic phase unless given artificial respiration. Most of the drugs are more potent in rats than in mice by this test (Swinyard et al., 1952).

Seizures have also been induced in rabbits with a current of 300 m.a. for 0·2 seconds and in cats with 400 m.a. for 0·2 seconds (Toman et al., 1946). The average duration of convulsion is 19 seconds in rabbits and 15 seconds in cats. These animals, however, have not found much favour with other investigators.

(4) Psychomotor Seizure Test.

Developed by Toman (1951) and designated the psychomotor seizure test (P.S.M.), this test is based on seizure evoked by low frequency stimulation.

It measures the ability of an anticonvulsant drug to protect mice from a seizure caused by unidirectional rectangular pulses (6 per second) of four times the threshold intensity, delivered through corneal electrodes for 3 seconds (Swinyard et al., (1953). Toman (1951) has delivered rectangular pulses of 50 m.a., 6 per second frequency and 1 millisecond pulse width (duration) for 3 seconds through a rigidly mounted pair of electrodes fitted with salt paste against which the eyes are gently pressed. The Utah group of workers (Brown et al., 1953; Goodman et al., 1953a; Swinyard et al., 1953) have instead evoked seizures by 0.2 millisecond pulses 6 pulses per second using 32 m.a. current for 3 seconds via corneal electrodes. A drop of 0.9 percent sodium chloride is put into each eye for good electrical contact. The animal has an initial appearance of having been "stunned". The posture is awkward but upright; forelimbs are often crossed and hindlimbs spread wide apart, and the tail is frequently held practically vertical. The stunning may be preceded by a few seconds of running with a rolling gait. Face and forelimb movements resemble "purposeful automatism". Catatonia is often present. The abnormal behaviour lasts on average for 25 seconds during which period it does not respond to painful or other stimuli. At the end of the seizure the animal suddenly resumes normal locomotion and exploratory behaviour. An animal is considered protected if it walks away normally within 7 seconds after the end of stimulation. The seizure resembles phychomotor epilepsy in its overt manifestations and E.E.G. pattern. Phenurone is the only compound to block psychomotor seizures at nondepressant dose levels in mice. Hence it has been suggested that the test may be valuable in screening drugs for clinical usefulness in psychomotor epilepsy. Brown et al. (1953), however, find no correlation between potency ranking of a drug by the psychomotor test and its clinical value. They find that drugs ineffective in psychomotor epilepsy (e.g. phenobarbitone) rank higher than phenurone. This, however, in no way detracts from the great value of this test as a tool for the study of a variety of neurophysiological phenomena associated with a cerebral seizure discharge and the effects of anticonvulsant drugs thereon (Toman, 1951).

Chemical Methods.

Albertoni (1882) has made the first attempt to analyse the efficacy of an anticonvulsant drug by means of convulsant agents. Landois, has applied creatine to the cerebral cortex of animals in an attempt to produce focal seizures by chemical means. Baglioni and Magnini (1909) have introduced the topical application of strychnine to induce seizures. Since then a large number of chemicals have been utilised for inducing seizures in experimental animals.

Mostly metrazol is employed for induction of chemical seizure. A brief mention will only be made of other chemicals used. Strychnine has been used in rats and mice by some observers (Sampson and Fernandez, 1939; Everett and Richards, 1944; Berger and Ludwig, 1950; Slater et al., 1952; Everett and Richards, 1952; Chen et al., 1956). Most of them have given a dose of 1.5-3 mg. subcutaneously. Berger and Ludwig (1950) have used a slightly different method. They give the anticonvulsant by intraperitoneal injection in mice and at the time of its peak action start an intravenous infusion of 0. 01 percent strychnine at the rate of 0.3 ml/min. They take the occurrence of persistant convulsions as the end point. The literature on the subject has been reviewed by Dusser de Barennie (1933).

Picrotoxin has also been used by some investigators (Berger, 1952; Everett and Richards, 1949, 1954; Sampson and Fernandez, 1939;) in doses of 7.5-15 mg./kgm. subcutaneously. Berger and Ludwig have used a 0.1 percent solution of picrotoxin by the technique described above. Thujone in olive oil, or as a 2 percent suspension in 6 percent gum acacia, has also been employed subcutaneously and intraperitoneally in rats, mice and rabbits (Sampson and Fernandez, 1939; Everett and Richards, 1944, 1952) in 200-500 mg./kgm. doses. Other drugs occassionally employed as convulsants include 20 percent camphor in sesame oil (Sampson and Fernandez, 1939); cocaine (Aird and ephedrine 100 mg./kgm. (Everett and Richards, 1952); and caffeine 300 mg./kgm. Strait, 1951); d-desoxy I. P. I. (Chen et al., 1956) etc.

Metrazol Threshold Tests.

Both rats and mice have been employed in these tests. In rats a dose of 70 mg./kgm. subcutaneously has been employed by the Utah group of workers (Goodman et al., 1946, 1949, 1953; Swinyard, 1949; and others.) Bogue and Carrington (1952) have employed 90 mg./kgm. of metrazol given intraperitoneally. Chen et al. (1951) have used 93 mg./kgm. metrazol subcutaneosly. Slater et al. (1952) and Gujral et al. (1956) have employed twice the LD50 of metrazol as convulsant dose. This dose exceeds LD99 by 50-75 percent Marshall and Vallance (1955) have used only 60 mg./kgm. of metrazol. In mice the Utah group (Goodman et al., 1953; Grewal et al., 1954; Swinyard et al., 1952, 1953; and others) have employed 85 mg./kgm. of metrazol subcutaneously. Berger et al. (1950) have used a 0.5 percent solution of metrazol by the technique described above, taking the first twitch, pseudoconvulsion or persistant convulsion as the end point. Everett and Richards (1944) and

Toman et al. (1952) have employed 100 mg./kgm. metrazol subcutaneously and Brodie et al. (1955) 120 mg./kgm. subcutaneously.

The test is carried out by making the metrazol injection approximately 10 minutes before the anticipated peak action of the anticonvulsant and observing the animals for the occurrence of seizures. A threshold convulsion is an episode of clonic spasms persisting for at least 5 seconds. Absence of even a threshold convulsion during the following sixty minutes is taken as the end point.

Maximal Metrazol Seizure Pattern Test (M.M.S.)

(Goodman et al., 1953a & b ; Grewal et al., 1954; Swinyard et al., 1953). The test measures the ability of drugs to alter the pattern of seizures induced by the rapid intravenous injection of CD97 (38 mg./kgm. as 0.5 percent aqueous solution) of metrazol in the dorsal tail vein of mice. In order to ensure seizures of uniform character, the volume of metrazol solution injected does not exceed 0.25-1 ml. and the duration of injection 4 seconds. The animal is considered protected if the drug prevents the appearance of the hind leg extensor component of the seizure. Marshal and Vallance (1955) have induced maximal seizures in mice using a dose of 60 mg /kgm. of metrazol.

Goodman et al. (1953 b) have compared the pattern of maximal seizures evoked by metrazol and supramaximal electroshock in mice. They are of the opinion that the M.M.S. test is not suitable as a routine anticonvulsant assay procedure, but a study of its properties will contribute to the understanding of maximal seizures and of the mechanism and spectrum of action of anticonvulsant drugs

Other Assay Techniques.

1. *Chronic Focal Seizures.* Speransky et al. (1926) have introduced the method of focal freezing of the cerebral cortex to produce chronic epileptogenic lesions in dogs. The method has also been used later by Keith et al. (1944). Kopeloff et al. (1944) have produced focal lesions by implantation of alumina cream and other substances in dogs and monkeys. The method has been used only sporadically, although "it offers a useful method, particularly when combined with EEG studies" (Toman and Goodman, 1948).

2. *Agene Convulsions in Dogs.* In studies of canine epilepsy produced by administration of agenised (NCl_3 treated) wheat protein and other proteins-zein, casein etc.—a great similarity to human epilepsy has been observed in physical manifestations and E.E.G. findings (Erickson et al., 1947; Silver et al., 1947) and also in a number of biochemical changes in blood (Belford and Bonnycastle, 1950). The ingestion of 3.0 gm./kgm. of agenised zein (30 gm. NCl_3/kgm.) produces convulsion within 18 hours. Phenobarbitone and paradione can prevent the occurrence of convulsions at nontoxic dose levels. Tridione affords protection only in toxic doses. Dilantin on the other hand aggravates the effects of agenised gluten (Redomski and Woodland, 1940). The probable mechanism of this is discussed by Belford and Bonnycastle (loc. cit).

3. *Semicarbazide Convulsions.* Semicarbazide in doses of 250 mg./kgm produces repeated maximal seizures for 4 hours after a latent period of one hour. These seizures are not antagonised by effective doses of Dilantin, pentobarbital, phenindamine, citrate, glutamate, acetate and histaminase. Acetone, Phenurone, Tridione, phenobarbitone, *a*-ketoglutamate, pyruvate and glucose are effective antagonists in descending order (Jenney and Lee, 1951). Jenney and Lee conclude that convulsions are probably due to carbonyl trapping leading to a concomittant interference with carbohydrate metabolism.

4. *Audiogenic Seizures.* Induction of audiogenic seizures in rats, first described in 1924, has received considerable attention since then (Finger, 1947). Work done on ability of various agents to prevent these seizures has been for the most part qualitative (Cohen and Karn, 1943; Griffith, 1942a; Shohl, 1944; and Corn et al., 1955). The audiogenic stress represents the exaggeration of a normal element (i. e. sound) in the rat's environment rather than the introduction of a qualitatively foreign stimulus as in electrical and chemical seizures.

An electric bell mounted in a sound roof chamber with a double paned glass top for observations has been used by Greenberg and Lester (1953). Rats fasted for 16 hours are individually exposed to stress. A reaction is considered positive as soon as active leaping phase or tonic clonic phase appears (Greenberg and Lester, 1953; Smith, 1941). Goodell (1955) has induced minimal and maximal audiogenic seizures in mice by a mixed frequency air whistle (520 K.C.). The seizure is preceded by several seconds of wild running. Once initiated the wild running is totally dependent on, the minimal seizure is variably dependent on and maximal seizure totally independent of the continuation of sound stimulus. The etiology of these seizures has been variously contributed to conflict neurosis, overloading of C. N. S., nutritional deficiency, and combination of these (Finger 1947; Corn et al., 1955). Several reports (Griffiths, 1942b; Maier, 1943; Maier and Glaser, 1946) have suggested a genetic component in susceptibility to seizures. The gross manifestations of audiogenic seizures bear similarities to grand mal attacks. Lindsley et al. (1942) found that during convulsons many features in common with E. E. G. in human convulsive seizures could be recognised. Whether these qualities of the seizures give it an advantage over electroshock and chemical methods is a debatable point (Corn et al., 1955).

Although so many assay methods are available, for several reasons new tests should be continuously sought. Each new method sheds additional light on the nature of the convulsive process and the mechanism of anticonvulsant drug action. New chemical series containing potentially effective antiepileptics may not be adequately measurable by animal assay techniques now in use. Finally, specificity for particular types of epilepsy and for sensory, psychic and motor components of seizures may perhaps be better gauged by newer methods of screening.

Neurotoxicity Tests

In as much as the measure of usefulness of an antiepileptic drug is not its absolute potency but its therapeutic index (margin of safety), the Utah group of workers have expressed the specificity of each drug measured by each assay method as a 'protective index' which represents a laboratory approximation to the therapeutic index. The protective index is obtained by determining the toxic dose (TD 50) for each drug and dividing it by the effective dose (ED 50) of that drug for each test.

Acute toxicity of anticonvulsant drugs is invariably manifested in some form of neurological abnormality (Swinyard et al., 1952). Each animal is examined for its neurological status before and after the administration of the drugs. The following 5 tests are used by these workers for disclosing minimal neurological defiicit.

1. *Positional Sense Test.* Neurological deficit is indicated by inability to rapidly correct the abnormal position if the hindlimbs of the rat are gently lowered over the edge of a table.

2. *Righting Test.* Neurological dificit is indicated by inability to rapidly correct the abnormal posture if a rat is placed on its back.

3. *Gait and Stance Test.* Neurological deficit is indicated by a circular or zig-zag gait, ataxia, abnormal spread of legs, abnormal body posture, tremor, hyperactivity, lack of exploratory behaviour, somnolence, stupor, catalepsy etc.

4. *Muscular Tone Test.* Neurological deficit is indicated by a loss of skeletal muscle tone characterised by hypotonia or flaccidity.

5. *Equilibrium Test.* This test is especially useful in mice. If a normal mouse is placed on a narrow edge, e. g. rim of a cage or bread pan, it can maintain its equilibrium and walk along the rim. Neurological deficit is indicated by inability to do so.

Abnormal neurological status discovered by any of these 5 tests is taken as the end point for TD50 determination. However, if other side effects, e. g. hematuria, hyperpnoea, crystalluria etc., consistently appear at lower doses—cf. mysoline (Goodman et al., 1953)—they are taken as the end point.

B. CLINICAL ASSAY

Goodman et al., (1949) rightly emphasize that the ultimate value of a new anticonvulsant drug must be established by clinical trial in epileptic patients. The difference in response of different convulsive disorders to a particular medication makes accurate diagnosis an absolute prerequisite for adequate evaluation of the clinical worth of a new drug. Certain complica-

tions of clinical trial may tend to discriminate for or against a particular anticonvulsant. For example the effects of addition of another agent to an established schedule of medication may give an exaggerated impression of the separate worth of the added drug if synergism occurs. Again the tendency to reserve clinical trial of new agents for refractory patients whose seizures have resisted all ordinary therapy places an undue burden of proof on the test agent (Merritt and Brenner, 1947).

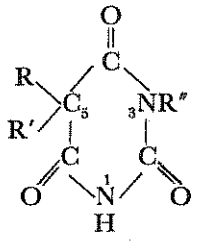
Goodman et al., (1948) have also used another method of clinical assay. They have measured the ability of drugs to modify seizure patterns in nonepileptic patients undergoing electroshock therapy for psychiatric disorders. Control seizure patterns are compared with those obtained after three days treatment with various dose levels of drugs and several days after withdrawl of the medication. Hemphill and Walter (1941), Kalinowsky and Kennedy (1943) and Garciadiego et al. (1944) also have studied the effects of antiepileptic drugs on electroshock seizures in man. They have, however, concentrated their attention on changes in threshold and not on changes in seizure pattern.

Kaufman and Watson (1948) and Ziskind et al. (1946) have used metrazol for activating E. E. G. dysrhythmia in epileptic patients and this has also permitted observations on anticonvulsant drug action. Goldstein and Weinberg (1940) and Frost (1939) have used metrazol seizure threshold test to evaluate anticonvulsant drug action in patients.

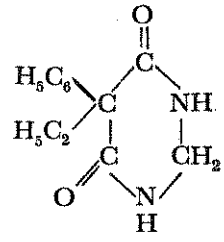
STRUCTURE ACTIVITY RELATIONSHIP

The structure-activity relationship (SAR) of the anticonvulsant drugs has not been adequately elucidated despite numerous studies in this field. The subject has been reviewed by Merrit and Putnam, 1940a; Rosa, 1942; Toman and Goodman, 1948; De Jong, 1948 & 1949; Ware, 1950; Cheymol, 1950; Toman et al., 1952; and Toman and Taylor, 1952. The extensive work of Merrit and Putnam (1937-40), which culminated in the discovery of the clinically useful diphenylhydantoin, seems to be the beginning of a systematic search for more effective, less toxic and less hypnotic compounds. The major chemical nuclei from which most of the effective drugs are derived include the 6- and the 5-membered cyclic diureides (barbiturates and hydantoinates), some of their congeners (oxazolidin-2,4-diones, and succinimides) and some acyclic monoureides (phenurone). In addition several simple compounds like alcohols and diols, ketones, sulphones, amides and ureas (vide infra) also show some anticonvulsant activity. Recently the role of the "essential urea moiety" has also been questioned by the reduction of the C^2-carbonyl into the corresponding methylene group thus producing the desoxy analogues mysoline (Bogue and Carrington, 1953) and the glyoxaline SKF 2599 (Goodman et al., 1954).

The chemical structures of the more common anticonvulsant drugs are given below:

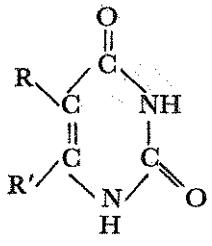


barbiturates

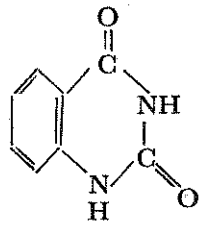


2-desoxyphenobarbital
(mysoline)

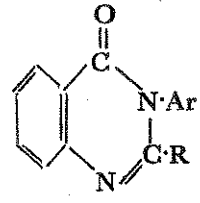
	R	R′	R″
phenobarbital :	C_6H_5	C_2H_5	H
mephobarbital :	C_6H_5	C_2H_5	CH_3
metharbital :	C_2H_5	C_2H_5	CH_3



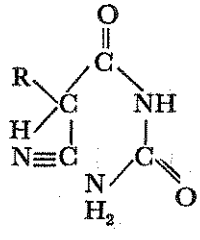
uracils



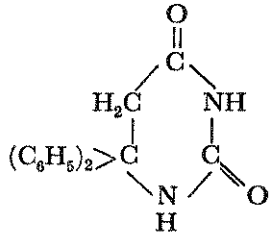
benzouracils



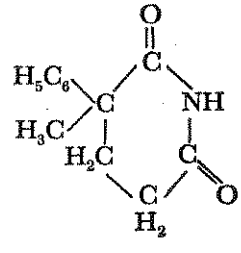
quinazol-4-ones
(QZ-2 etc.)



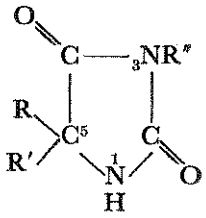
α-cyanoureides
(uracil intermediates)



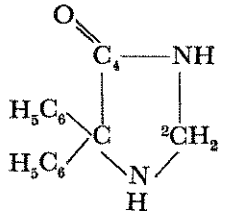
diphenyldihydrouracil
(homodilantin)
inactive



methylphenylglutarimide
(homosuccinimide)
active

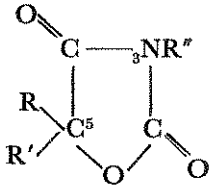


hydantoins

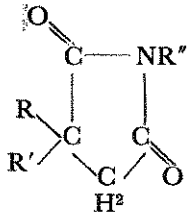


2-desoxydilantin
(tetrahydroglyoxalin-4-ones)

	R	R′	R″
phenytoin :	C_6H_5	C_6H_5	H
mesantoin :	C_6H_5	C_6H_5	CH_3
thiantoin :	C_6H_5	2-thienyl	H



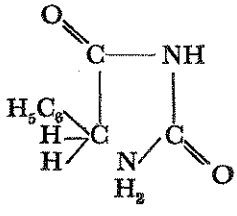
oxazolidin-2,4-diones



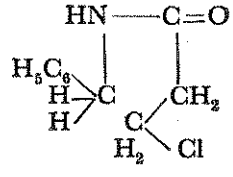
succinimides

milontin : R=C_6H_5; R′=H; R″=CH_3

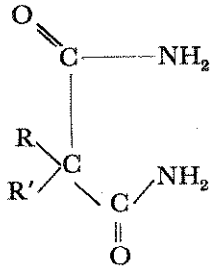
	R	R′	R″
tridione :	CH_3	CH_3	CH_3
paradione :	CH_3	C_2H_5	CH_3
malidone :	CH_3	H	$-CH_2-CH=CH_2$
epidon :	C_6H_5	C_6H_5	H



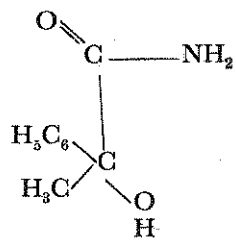
phenurone



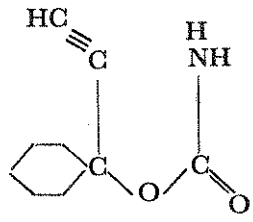
hibicon



malondiamides

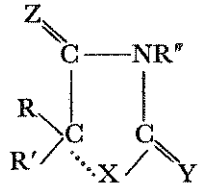


atrolactamide



valmid type urethanes

Thus most of them appear to have been developed around the basic structure



where X may be the remaining structure of barbituric acid, nitrogen as in hydantoins, oxygen as in oxazolidindiones, carbon as in succinimides, or the terminal nitrogen of the phenylacetylurea if no C—N bond is formed. This molecular make up reveals a striking structural similarity between these compounds. They all contain the common root-structure $\begin{matrix} R \\ R' \end{matrix}\!>\!\overset{5}{C}\!-\!\overset{4}{C}O\!-\!\overset{3}{N}(R'')\!-\!\!-\overset{2}{C}O\!-$, where R and R′ =H, alkyl or aryl and R″=H or alkyl. Those which are good threshold-stabilizers and are particularly effective against grand mal possess a resonant aromatic nucleus, ordinarily a phenyl group, at R or R′. Possibly this is needed for electronic activation of this centre and/or some favourable conformation (constellation) essential for the drug-cell receptor complex. A short alkyl at R″ (usually methyl) may result in some loss in potency for threshold-stabilization with an increased ability to raise the threshold. The desoxy compounds like mysoline and SKF 2599 (loc.cit.) contain the grouping $\begin{matrix} R \\ R' \end{matrix}\!>\!C\!-\!CO\!-\!NH\!-\!CH_2\!-$, and those like the QZ-2 type quinazolones $\text{arom.}\overset{\diagdown}{C}\!-\!CO\!-\!N(Ar)\!-\!C(R)\!=$. Hibicon, with $\begin{matrix} R \\ R' \end{matrix}\!>\!C\!-\!NH\!-\!CO\!-\!CH_2\!-$, is an example of the "reversed amide analogue" of the desoxy compounds (cf. reversed carboxyl analogue of acetylcholine, Barlow, 1955, page 122).

A brief resume of the structure-activity studies in the individual anticonvulsant groups is given below :

Barbiturates

Role of C^5-phenyl group. Free barbituric acid and its 5-methyl- and 5,5-dimethyl derivatives are devoid of hypnotic or antiepileptic activity. 5-methyl-5-ethyl compound is only weakly hypnotic and the 5,5-diethyl compound (barbital) is hypnotic but not anticonvulsant. The substitution of a phenyl for an ethyl group in barbital is the basis for the specific antiepileptic properties of phenobarbital, useful particularly in grand mal. Although in anaesthetic doses all the clinically useful barbiturates, and to some extent other hypnotics as bromide, chloral, ethyl alcohol, propyleneglycol, paraldehyde and avertin (Tainter et al., 1943) are capable of inhibiting epileptic convulsions, phenobarbital in sedative doses was found to be more effective in preventing major electroshock seizures (Merrit and Putnam, 1938). This selective action of phenobarbital, which is not shared by the non C^5-phenyl barbiturates except metharbital, was shown by Keller and Fulton (1931) to be due to its corticomotor depressant activity. The mechanism which raises convulsant threshold is different from that producing hypnosis since nonhypnotic doses are often effective and also because amphetamine counteracts the hypnosis without abolishing the anticonvulsant action. (For distinction between hypnotic and anticonvulsant actions, see *page* 94-95). 5-Phenyl-5-alkyl barbiturates are examples in which these two actions have been resolved. In this series 5-phenyl-5-butyl compound is the most potent anticonvulsant with little hypnotic action. Hypnotic activity is maximal in compounds with small alkyl groups (Alles et al., 1947).

The C^5-phenyl group can be replaced by naphthyl (Merrit and Putnam, 1945; Long, 1948) or by phenanthryl groups (Lustig and Persch, 1954). Introduction of -OH groups in the benzene ring or its saturation to produce the alicyclic analogues (Merrit, Putnam and Bywater, 1945) abolishes activity. 5-(p-Hydroxyphenyl)-5-ethyl-barbituric acid has been isolated as an inactive metabolite of phenobarbital (Algeri and Mcbay, 1956; Butter, 1956). Introduction of alkoxy, aryloxy or thioalkyl groups as side chain in the C^5-alkyl in both the barbiturates and the thiobarbiturates diminishes activity (Merrit, Putnam and Bywater, 1945). On the other hand, unsaturation in the C^5-alkyl chain enhances antiepileptic activity. 5-Phenyl-5-crotyl compound is more potent than the corresponding butyl compound (Wyngaarden et al., 1949). This is in line with the enhancing of the hypnotic activity in hexenyl-, pentenyl-, butenyl- and allylbarbiturates. 5-Ethyl-5-(1-methyl-1-butenyl) barbituric acid (vinabarbital or delvinal) has also been shown to possess anticonvulsant activity (Davidoff and Doolittle, 1944).

A second phenyl group on C^5 diminishes anticonvulsant activity (Knoefel and Lehman, 1942).

Role of N-alkylation. N-methylation of 5,5-dialkylbarbituric acids confers anticonvulsant activity (trimethyl barbituric acid, 3-methyl-5-methyl-5-ethyl-barbituric acid and metharbital) while that of 5-phenyl-5-alkyl compounds reduces their antielectroshock effect and enhances their antimetrazol potency

(mephobarbital) (Toman and Goodman, 1948). Metharbital and mephobarbital are also less sedative than their non N^3-methyl analogues (Cohen and Meyerson, 1942; Brown and Smith, 1953; Smith, 1953). Methylation of both nitrogens (N^1 and N^3) tends to produce convulsant compounds with undesirable properties (Goodman and Gilman, 1955). N-Allyl-5,5-diallylbarbituric acid resembles dilantin in the anticonvulsant spectrum (Sandberg, 1951.)

Thus a C^5-phenyl and N-methyl, individually as well as in conjugation, may possibly have some significant role to play in depressing the electrical excitability of the motor cortex and preventing the repetitive firing in supramaximally stimulated peripheral nerves.

Role of Carbonyl groups. The conversion of C^2-carbonyl (of the urea moiety) into its thio and imino analogues ($>C=0 \rightarrow >C=S$ and $>C=NH$) adversely affects the antiepileptic properties. Its reduction to a methylene group, however, does not alter the spectrum of anticonvulsant activity (Goodman et al., 1953). Mysoline is less effective than phenobarbital, but it is particularly potent in abolishing the tonic component of maximal (tonic clonic) electroshock seizures. It is non toxic and safe anticonvulsant though its activity is accompanied by sleepiness. C^4-keto seems to be essential for activity. The reduction of C^6-keto gives uracils some members of which show antielectroshock activity (vide infra). Removal of C^6-keto leads to the corresponding hydantoins in which the anticonvulsant action is retained, though its pattern and the hypnotic action are modified.

Hydantoinates

Hydantoinates, the five membered cyclic diureides or glycolylureas, are, in general, more predominantly anticonvulsant than the barbiturates or malonylureas. They are threshold-stabilizers and seizure-limiters.

C^5-phenyl. At least one C^5-phenyl group is necessary for activity. Nirvanol, the hydantoin analogue of phenobarbital, is active in various types of convulsions particularly in rheumatoid chorea in children. It is too toxic and no longer in use. 5-Phenyl-5-methyl compound (the lower homologue of nirvanol) is also very toxic and causes a skin rash which is not exhibited by its dextro-form. This points to the importance of steric configurations in this series. Introduction of alkoxy, alkylthio, aryloxy and dialkylamino groups on the C^5-alkyl chain lowers activity (Henze and Magee, 1940; Ware, 1950, page 453-55).

In hydantoins C^5-diphenyl compounds have proved more useful. 5,5-diphenylhydantoin (dilantin) is very effective in grand mal and psychomotor seizures without producing hypnosis. This selective depressant action on the motor cortex without appreciable effect on the sensory areas is shared neither by phenobarbitone, which acts on both the areas, nor by diphenyl barbiturates which are not used due to their toxicity and side effects. Thus dilantin is another example where the two effects have been resolved (cf. 5-

phenyl-5-butylbarbiturate). Dilantin is also effective in psychomotor seizures (though it is of limited use in practice) against which phenobarbital is ineffective. Diphenylenehydantoin resembles dilantin but produces skin rash (Knoefel and Lehman, 1942; Merrit and Putnam, 1945a and 1947; Fabing et al., 1947). Spirohydantoins (with cyclic ketones) also show some activity (Tiffeneau et al, 1943; Henze et al, 1947). 5-Benzhydrylhydantoin is active but too toxic (Henze et al, 1950). 5,5-Dianisyl compound is almost inactive (Mercier, 1950).

Phenyl groups can be replaced by other *isosteric* aromatic heterocyclic nuclei. 5-Thienyl-5-phenyl compound (thiantoin) is quite potent though no longer in use. 2-Pyridyl-, 8-quinolyl-, as well as dithienyl analogues are less effective while 5-quinotoxin hydantoin is inactive (McKee et al, 1944). Non-aromatic rings, as in 5,5-dipiperidyl compound, abolish activity (Mercier, 1950).

N-Alkylation. N-methylation broadens the anticonvulsant spectrum. Some of these N-methyl compounds are demethylated in the body. Mesantoin, the hydantoin analogue of mephobarbital or N-methylnirvanol, resembles dilantin in its anticonvulsant action. It is more sedative than dilantin. Skin rash, hematopoietic disorders and hepatic injury are among its toxic reactions and possibly arise from its demethylation in the body to nirvanol. N-allyl-5-phenylhydantoin and N-allyl-dilantin resemble dilantin in activity (Sandberg, 1951).

Carbonyl groups. Diphenylthiohydantoin ($>C^2=0 \rightarrow >C=S$) is devoid of activity (Knœfel and Lehman, 1942). The same is the case with 5,5-dimethyl-2-thio- and 5,5-dimethyl-2,4-dithiohydantoins (Henze and Smith, 1943). Reduction of the C^2-carbonyl (of the urea moiety) to methylene group produces glyoxalines. SKF 2599 (5,5-diphenyl-tetrahydroglyoxalin-4-one) resembles mysoline in being less potent but also less neurotoxic (Goodman et al., 1954; Wilfon et al., 1956). C^4-keto seems to be essential for activity.

Oxazolidin-2,4-diones

Structurally this nucleus is derived from the replacement of nitrogen (N^1) of the urea moiety in hydantoins by oxygen. They are, therefore, the oxy analogues of hydantoins. Oxazolidin-2,4-diones were originally investigated by Erlenmeyer (1938) for their hypnotic and CNS depressant action. A series of 5,5-dialkyl derivatives tested by Luton et al. (1941) showed the di-n-propyl compound (propazone) to be the most promising hypnotic of this class. 3,5,5-Trimethyl compound (trimethadione, tridione), synthesized by Spielman (1944) and investigated by Everett and Richards (1944) and Goodman, Toman and Swinyard (1946), was shown to be a potent analgesic and an anticonvulsant useful specifically against petit mal. It is the most potent antagonist to metrazol-induced seizures known so far. It can also antagonize electroshock seizures but is less potent than barbiturates and hydantoinates. It is also sedative. In this series small alkyl groups on C^5 result in a

decrease in hypnotic activity and an increase in analgesic and anticonvulsant effect. Longer alkyl groups as in 3,5-dimethyl-5-ethyl compound (paradione) (Spielman, 1944; Davis and Lennox, 1947; Everett and Richards, 1950; Swinyard et al, 1952; Brown, 1953) or 3-ethyl-5,5-dimethyl analogue do not seem to confer any greater clinical effectiveness against petit mal. Propazone likewise inhibits only metrazol convulsions. 3-Allyl-5-methyl derivative (malidone, aloxidine) is effective in petit mal without causing any hemeralopia or the glare phenomenon (Butter, 1952). N-Alkylation enhances the analgesic and particularly the anticonvulsant action. 5,5-Dimethyl derivative is devoid of any anticonvulsant activity (Swinyard et al., 1952; Butler, 1953).

C^5-Phenyl groups, on the other hand, confer anti-grand mal and antielectroshock activity. Thus 5,5-diphenyl compound (epidon, the oxy analogue of dilantin) is effective only in grand mal and not in petit mal irrespective of its oxazolidin-2,4-dione nucleus. Epidon resembles dilantin and has no activity against metrazol-induced convulsions (Toman and Goodman, 1948). The C^5-monophenyl derivative is superior to the diphenyl compound in raising the metrazol seizure threshold.

Replacement of the heterocyclic oxygen of tridione by sulphur gives the thio analogue of hydantoins. It is inactive (Burger, 1951, Vol. 1, page 149). 5,5-Dimethyl- and 5,5-diethyl-thiazolidin-2,4-diones possess anticonvulsant activity (Hazard et al, 1949; Marshall and Vallance, 1954). 5,5-Diethyl-oxazolidin-2,4-dione, however, possesses a little anticonvulsant activity.

Imides

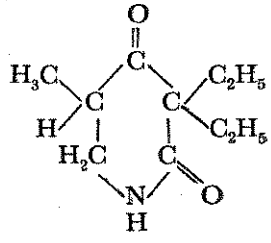
Imides have provided some better anticonvulsants than the acyclic amides. *a*-Phenylsuccinimide and its N-methyl derivative, milontin, have been investigated by Chen and coworkers (1951); Zimmermann, (1951); Millichap, (1952). They closely resemble other antiepileptic nuclei. Structurally succinimides can be derived from oxazolidin-2,4-diones and hydantoins by replacing the heterocyclic oxygen O^1 and nitrogen N^1 by CH_2. They are therefore the *carbon analogues* of these heterocycles. Milontin resembles tridione and is more effective against metrazol seizures. *a*-or β-methyl or ethyl derivatives are also more effective against metrazol than against electroshocks. In this series N-alkylation increases the potency and a methyl group is superior to other alkyl groups in this respect. *a-a*-Diphenyl and *a*-β-Diphenyl succinimides, on the other hand, are more effective against electroshock (cf. dilantin and epidon). In this series N-methylation decreases the potency. Marshall and Vallance (1954 and 1955) have investigated *a*-methyl α-phenylglutarimides. Their N-methyl derivatives are more potent. N-methylmaleicimide and 4,5-cyclohexenosuccinimides show only very feeble activity. β-Methyl-β-ethyl-glutarimide shows promise as specific barbiturate-antagonist (Shaw et al., 1954; Harris, 1955; Shulman, 1955).

Miscellaneous heterocyclic compounds

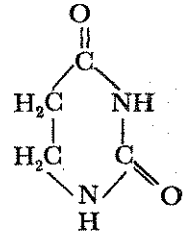
Hexahydropyrimidin-2,4-diones (*6-desoxybarbiturates or uracils*) resemble

hexahydropyrimidin-2,4,6-triones (*barbiturates*) and hexahydropyrimidin-4,6-diones (*2-desoxybarbiturates* or *mysoline analogues*) in possessing some anticonvulsant activity. Wenzel and Keplinger (1955) and Burckhalter and Scarborough (1955) showed that uracil, thymine (5-methyluracil), 6-methyluracil, other related oxypyrimidines and thiouracil had significant antielectroshock activity. They were inactive in metrazol convulsions. Thymine was better than uracil and 6-methyluracil. C^5-phenyl was not necessary in the uracils (*cf. barbiturates*). In fact both the 5-phenyl compound and the 5,5-diphenyl compound (homodilantin) were inactive. 5-Benzyl- and the 6-phenyl analogues did have some activity. 1-Methyluracil was inactive while the 1,3-dimethyl compound, particularly 1,3-dimethyl-5-butyl-(or 6-hexyl) compound was quite active. They were also toxic. Unsubstituted quinazolin-2,4-dione (*5,6-benzouracil*) was inactive in both the electro and the chemoshock seizures. Its 1,3-dimethyl analogue affords substantial protection in electroshock seizures but is very weak against chemo-shocks. All the active compounds were reported to be of low activity. 2-Alkyl-3-aryl-quinazol-4-ones, on the other hand, have been shown by Gujral and coworkers (1957) to be fairly potent anticonvulsants in raising the threshold of metrazol convulsions as well as in modifying the supramaximal seizures (cf. spirobarbiturates, spirohydantoins and diphenylenehydantoins). They are of low toxicity.

Anticonvulsant activity has also been observed in some diketopiperidines as 3,3-diethyl-5-methyl-piperidin-2,4-dione or methyprylon (Schallek et al., 1956). It was recently introduced by Pellmont et al. (1955) as a non-barbiturate hypnotic. It is more effective against metrazol seizures than against electroshocks.



methyprylon



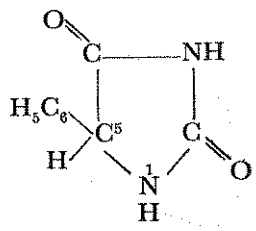
5,6-dihydrourancil

Structurally these compounds can be derived from 5,6-dyhydrouracils by replacing the heterocyclic N^3 (of the urea moiety) by $—CR_2$ (cf. hydantoins and oxazolidin-2,4-diones vs. succinimides). The activity of these *carbon analogues* appears to deempasize the essential role of the urea moiety (cf. C^2-desoxy antiepileptics).

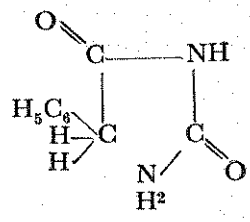
Likewise several benzazoles as benzoxazoles (Bywaters, et al., 1945) and benziminazoles (Goodman et al., 1943; Toman et al., 1946; Toman et al., 1950; Domino et al., 1951 and 1952; Funderburk, 1953) have been shown to possess anticonvulsant activity.

Acyclic Compounds

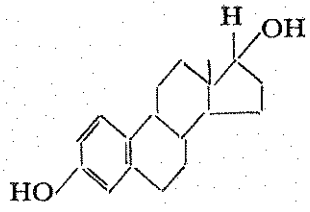
Ureides. Although phenylacetylurea (phenurone, phenacemide) is the open chain analogue of 5-phenylhydantoin with ring opening at N^1—C^5 bond, the acyclic compound does not depend for its activity on its cyclization to the hydantoin. The hydantoin also does not owe its activity to the opening of the ring. It is, therefore, neither a precursor nor a degradation product of the hydantoin (cf. estradiol vs. diethylstilbestrol).



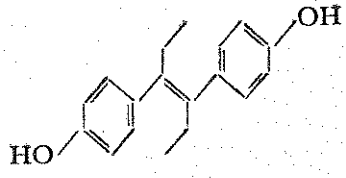
5-phenylhydantoin



phenurone



estradiol



diethylstilbestrol

Phenurone has a broad anticonvulsant spectrum. It has high potency in metrazol, strychnine as well as in electroshock convulsions coupled with a specific effect in psychomotor seizures. The activity resembles that of 5-phenyl-barbiturates; a short C^5-alkyl group like methyl or ethyl increases the activity while a second phenyl group abolishes it (Knoefel and Lehman, 1942; Swinyard and Toman, 1950; Everett and Richards, 1952). Thus the *a*-ethyl compound, $C_6H_5.CH(C_2H_5).CO.NHCONH_2$, is twice as potent and better tolerated as phenurone (Gold et al., 1952; Frommel et al., 1952), whereas the diphenyl compound is totally inactive (possibly due to its insolubility). The *a*-ethyl compound is more sedative like phenobarbital, is more active in electroshock and inactive in metrazol shock. The corresponding cyclohexyl and the thienyl analogues are inactive; aliphatic substituents on the amidic nitrogen likewise reduce activity (Everetts and Richards, 1952).

a-Cyanoureides, $RCH(CN).CO.NHCONH_2$, intermediates in the synthesis of uracils (loc. cit.) are also active though too toxic (Wenzel, 1952).

A feeble anticonvulsant activity has also been found in the related biurets, $R_2CH.CO.NHCONHCONHR$, and allophanates, $ROOC.NHCONH_2$ ($R = C_2H_5(CH_3)_2C$-, $CH_3(C_2H_5)_2C$-, $C_6H_5(C_2H_5)CH$-, etc.). (Allophanic acid,

$HOOC.NHCONH_2$, is the lower homologue of hydantoic acid, $HOOC.CH_2$-$NHCONH_2$). 1-Diethylacetyl-5,5-cyclopentamethylene-biuret, in contrast to phenobarbital and dilantin, prevents cocaine convulsions (Anderson and P'an, 1941) Dithiobiuret is effective only in toxic doses. Phenylsemicarbazide, $C_6H_5.NHNHCONH_2$ or anilinourea, is a feeble anticonvulsant (Burger, 1951, Vol. I, page 143), while semicarbazide, $H_2N.NHCONH_2$ or aminourea, and thiosemicarbazide, $H_2NNHCSNH_2$ or aminothiourea, are convulsants and produce photogenic seizures (Jenney and Lee, 1951; Stephens, et al., 1952; Pfeiffer, 1955, page 168).

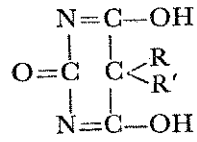
Amides. Recently some amides have been found to possess anticonvulsant activity. Jenney and Pfeiffer (1956) studied the SAR of mandelamides. Atrolactamide was found to be the most potent in this series. It represents a truncated portion of the common root-structure of the conventional antiepileptic nuclei which has retained a wide spectrum of anticonvulsant activity. It is effective in grand mal, moderately effective in psychomotor and mildly effective in Jacksonian focal seizures (Stamps et al., 1952). But it is toxic. Long alkyl groups on N reduce toxicity and also activity. Replacement of the phenyl by alkyl groups abolishes antielectroshock activity and enhances the antimetrazol potency. *a*-Aminodiphenylacetamide has only very weak activity (Billman, et al., 1945). Another amide is hibicon (N-benzyl-β-chloropropionamide, $C_6H_5CH_2NH.CO.CH_2CH_2Cl$) which was investigated by Kushner, et al., 1951; Harned, 1953; Quevauviller and Garcet, 1953. It is effective both in electro- and metrazol-seizures and affords adequate relief in grand mal though it is less effective in psychomotor epilepsy and is of no value in petit mal (Hawkes, 1952). It has no analgesic or sedative properties and its anticonvulsant activity is of the same order as that of dilantin though with a wider margin of safety. Its benzylamine portion, $C_6H_5CH_2$-NH.CO—seems to be more important than the β-haloalkyl chain.

Some *a-a*-dialkylmalonamides also show anticonvulsant activity in experimental animals without producing hypnosis, while their dehydration products malononitriles seem to be of promise in some psychiatric disorders (Hartelius, 1950).

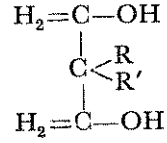
Many urethanes, $(CH_3)_2CH.O.CONH_2$ and $(CH_3)_3C.O.CONH_2$ etc. (Long, 1948) are also active. Among the several carbamic esters of unsaturated carbinols a recent addition is Valmid, $C_6H_{10}.(C{\equiv}CH).O.CONH_2$ or ethinylcyclohexylurethane. It is quite potent anticonvulsant effective against both the electro- and chemoshocks (Swanson, 1956). It was originally introduced as a quick and short acting hypnotic of low toxicity (Langecker et al., 1953; Gruber et al., 1954).

Diols and unsaturated carbinols. Several 2,2-disubstituted-1,3-propandiols have been examined by Berger and Ludwig (1950–52) and Slater et al. (1952). These compounds have no apparent structural similarity to the conventional anticonvulsants and do not contain any *"urea moiety"*. They may, however, resemble the *enolic form* of the *"malonyl portion"* of the

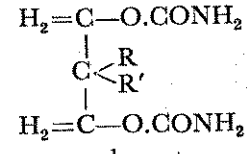
barbiturates (cf. atrolactamide). The 2,2-diethyl compound (prenderol, DEP) is a strong anticonvulsant effective against chemoshock (metrazol, strychnine and picrotoxin) in nonhypnotic doses. (The next higher homologue, $CH_2OH.CH_2.C(C_2H_5)_2.CH_2OH$ or 2,2–diethyl–1,4–butandiol is a convulsant). The 2,2-diphenyl compound, on the other hand, is effective in electroshock seizures. Both these compounds have only a short duration of action. Their diacetates and carbamates are less intense but longer acting while the 1,3 dioxan-2-ones are only weak and short-acting compounds.



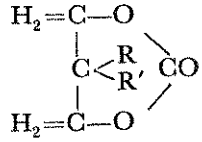
barbiturates (?)



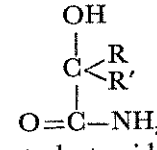
diols



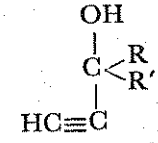
carbamates



1,3-dioxan-2-ones



atrolactamide



unsaturated carbinols

Certain unsaturated carbinols (Margoline, 1951; Schaffarzick, 1952; Pan et al., 1953; Swinyard et a.l, 1953; Marshall and Vallance, 1954) have also been found to possess anticonvulsant activity. The ethyl-vinyl compound ($R=C_2H_5$; $R'= -CH=CH_2$) is more potent than the methyl-ethyl compound ($R=CH_3$; $R'=C_2H_5$, dormison or methyl-parafynol). They are effective in electro- and metrazol-shocks and are also hypnotic. Meprobamate (miltown isomer) 2-methyl-2-n-propyl-1,3-propandiol dicarbamate (Selling, 1955; Borrus, 1955; Berger et al, 1956) is another anticonvulsant of this series. They are also used as tranquilizing agents and as interneuronal blocking agents related to mephenesin for their muscle relaxant properties.

Drugs employed in other hyperkinetic states

The mass of anticonvulsant drugs acts in a general manner, but some are specially effective against convulsions of a particular origin (e.g. convulsions produced by strychnineor Parkinsonism). Mephenesin and glyketal which specifically act on the spinal cord, also show some anticonvulsant activity. Structure–activity studies have indicated that their anticonvulsant and the muscle relaxantproperties are separable. These drugs are used primarily as centrally acting muscle relaxants and so are not included here. Prenderol (DEP) has been included above because it is also effective higher up the CNS and also because its anticonvulsant activity is relatively more prominent than that of mephenesin.

The common anticonvulsant drugs discussed above do not appear to affect the centres concerned in Parkinson's disease. Drugs like parpanit,

diparcol (diethazine) and artane which are specifically useful in Parkinsonism also show some anticonvulsant activity. Parpanit, for instance, can antagonize chemoshock seizures produced by nikethamide, strychnine and DFP in animals and electroshock in man. They are spasmolytics and are not included here.

Some Miscellaneous Compounds

Several simple ketones (Long, 1948; Spielman et al., 1948), ketone derivatives (Slater et al., 1952), complex ketonesas fluorenone (Knoefel and Lehman, 1942), alkyldiones (Wenzel and Koff, 1956) and sulphoxides, sulphones, amides and ureas (Long, 1948) also show a weak anticonvulsant activity. The anticonvulsant properties of the following compounds do not warrant any detailed description: 1. *Bromides* (Merrit and Putnam, 1938; Stone, 1940; Toman et al., 1946; Grewal et al., 1954; Barlow, 1955; Chakravarti, 1956); 2. *Glutamic acid* (Price et al., 1943; Goodman et al., 1946); 3. *Sulpha drugs* like prontosil, neoprontosil (the azo dyes Vital Red and Brilliant Vital Red). These cause acidosis and therefore their effect would be similar to that of ketogenic diet in epilepsy (Cobb et al., 1938 and 1940; Osgood and Robinson, 1938; Ronchetti, 1940); 4. *Diamox* which possibly acts through the inhibition of brain carbonic anhydrase, cf. sulpha drugs, (Mann and Klilin, 1940; Millichap, 1954 and 1955; Ansell and Clark, 1956; Bergstrom, 1956, Lombrosso, 1956); 5. *Several steroids* (Mc-Quarrie, 1942; Wycis and Spiegel, 1945); 6. *Amphetamine* and related amines; 7. Xylocaine (Bernhard et al., 1955); 8. Phenylcinchoninic acid or *atophane* (Pollock et al., 1941); 9. *Chlorpromazine* (Courvoisier et al., 1953; Bertrand et al., 1954 and 1955; Gujral et al., 1956); and 10. *Reserpine* (Chen et al. 1954; Tripod et al., 1954; Schneider 1954; Schneider and Earl, 1954; Bianchi, 1956).

Finally, it is desirable to discuss those aspects of the SAR of the anticonvulsant drugs which require further studies. A major difficulty is the uncertainty that the drugs are active in the form in which they are administered. In addition, the effect on centres in the CNS may be complicated by other actions. Dilantin, for instance, has been shown to lower the permeability of the barriers between blood and brain and blood and CSF to cocain (Aird and Strait, 1951). This reduces the penetration of this substance to the CNS. The agent producing convulsions, if applied outside the CNS (as an injection of metrazol), might be similarly affected and so a false impression of the anticonvulsant activity would be obtained.

Anticonvulsant and hypnotic activities. Another difficulty involves the *overlapping* of the anticonvulsant and the hypnotic activities. Although many anticonvulsants do possess hypnotic action, the two properties are separable and have been resolved in a number of compounds like dilantin and 5-phenyl-5-butyl barbituric acid (vide supra). Still it has not yet been ascertained whether the two properties are associated with the same pharmacophore, if any, (cf. the overlapping of certain biological activities like the local anaesthetic, spasmolytic, quinidine-like antifibrillatory, antihistaminic and analgesic actions in substances containing the structural

unit, $Ar.CO.O.C_n.N<$. Any one of these can predominate under suitable structural environments). Some CNS depressants, on the other hand, do not posses any significant anticonvulsant activity. Reserpine, for instance, inspite of its CNS depressant action, is not effective in electro-or chemoshocks (Chen and Ensor, 1954; Tripod et al., 1954), though it protects rats against audiogenic seizures (Tripod et al., 1954; Schneider, 1954; Schneider and Earl, 1954). Reserpine lowers the threshold of the CNS to electrical stimuli and suppresses the antielectroshock effect of dilantin and phenurone while enhancing their general depressant effect (Chen and Ensor, 1954; Chen and Bohner, 1954). It nullifies the anticonvulsant activity of dilantin, tridione and phenurone against metrazol–induced convulsions (Bianchi, 1956).

In contrast to the general CNS depressants usually employed to quieten maniacs, the anticonvulsant drugs act on specific centres concerned with convulsions. The convulsant activity in the brain is associated with certain biochemical changes which have been imitated in isolated sections of cerebral tissues by the application of high and low frequency electric potentials (Anguiano and McIlwain, 1951). Such potentials cause an increase in the respiration of the tissues. As anticonvulsants like phenobarbital, dilantin and tridione can antagonize this increase in concentration expected to correspond to therapeutic doses (Forda and McIlwain, 1953), it seems likely that they stimulate some inhibitory processes at these centres. Whereas hypnotics like chloral, butabarbital, and urethane affect the stimulation caused by both the type of frequencies, dilantin and tridione are specifically effective against increase produced by *high frequency stimulation.* Phenobarbital was intermediate in character, being rather more effective against the effects of high-frequency stimulation rather than that produced by the low-frequency. These results reveal a difference between the anticonvulsants and the general CNS depressants and make it easy to distinguish between the two types of activities. No such clear cut difference in the structural make up of the molecule which could be associated with the two separate activities is known so far.

Type of anticonvulsant activity. It is not yet clear what particular structural features are associated with a *specific type* of anticonvulsant activity. The common anticonvulsant drugs have recently been shown to fall into two classes (Goodman et al., 1953). The three hydantoins, dilantin, mesantoin and thiantoin, as a class, are much more potent in modifying the maximal electroshocks (MES) than the maximal metrazol shocks (MMS); they excel in the inhibition of seizure-spread but are relatively ineffective in elevating seizure-threshold. Phenobarbital, mephobarbital, tridone, paradione and phenurone, as members of the other class, are, on the other hand, much more potent in modifying MMS than MES; they possess both mechanisms of anticonvulsant action. (Dilantin is effective in preventing threshold-lowering and repetitive discharges produced by repetitive stimulation of peripheral axons. It is therefore a *threshold-stabilizer* and a *seizure-limiter.* Tridione is notable as a *thershold-raiser* for central neurones, but is relatively poor in

ability to modify seizure pattern or otherwise show threshold-stabilizing properties (Toman, 1955).

Inhibition of seizure spread is probably paramount for the drug induced modification of MES whereas a large component of chemoshock threshold elevation is important for the drug induced modification of MMS (Goodman et al., 1953).

Physicochemical mechanism of action. It appears a wide variety of compounds possess anticonvulsant activity. If one includes also the simpler substance like the ketones, sulphones and sulphoxides studied earlier by Putnam and Merrit (1941), there is a temptation to conclude that some anticonvulsant effects are likely with any substance having a lipid soluble moiety and a reactive nonterminal negative group not more than two carbons removed from this moiety. It seems unlikely that there should be a specific basic skeleton for all the known anticonvulsant structures. In the case of optically active compounds (mesantoin, nirvanol) the isomers do show some differences in potency and side effects but the activity remains in both the isomers (Toman, 1955), It is therefore possible that the anticonvulsant action may depen d, like that of the general CNS depressants, on a *physicochemical* process of transport coupled with an action on a particular enzyme, the nature of the enzyme being different at the various centres (Barlow, 1955).

Lastly, as the features of chemical structure responsible for *side effects* of the anticonvulsant drugs are relatively unknown, it is not possible to foresee the prohibitive toxic side-reactions peculiar to the human species. The measure of usefulness of an agent is therefore not its absolute potency but its therapeutic index. Hence the ultimate value of an anticonvulsant drug can be determined only in the clinical trials.

ANTICONVULSANT DRUGS AND MEASURES

Bromides

The actions of bromides, the oldest of the modern antiepileptic drugs (Locock, 1857), on the C.N.S. were recognised in 1850 when Huette published a report of bromide intoxication. The bromides introduced an era in which the greatest emphasis was placed on the use of sedative drugs (Spratting, 1904). Though largely supplanted by other drugs they are still sometimes used in the treatment of pure grand mal seizures. They are not useful in psychomotor seizures even though they raise the threshold for psychomotor seizure in rats (Grewal et al., 1954), and usually make petit mal worse (Lenox, 1940).

Little definitive work using modern neurophysiological technics has been done to elucidate antiepileptic action of bromides. In doses causing neurotoxicity bromides modify response to metrazol or electroshock (Meritt and Putnam, 1938; Toman et al., 1946) and the therapeutic index is much lower than for other drugs (Grewal et al., 1954). The exact mechanism of action is obscure but it is unrelated to displacement of extracellular chloride by bro-

mides (Goodman et al., 1949) and bromide ion itself is the active pharmacologic agent in causing C.N.S. depression (Hiatt, 1939). Barlow and Ing (1955) believe that they act by stimulating inhibitory processes in the brain. Chakravarty et al. (1956) have correlated the anticonvulsant effect of bromides with intracellular electrolyte and acid base changes, and have explained the action of bromides by the efflux of brain cell sodium secondary to an inhibition of brain carbonic anhydrase.

Potassium and sodium bromides (in doses upto 60 grains a day) are seldom used as they produce untoward effects, like, acne, foetid breath, brown furred tongue, salivation, constipation, mental confussion, lethargy, forgetfulness, impotency etc. and as better anticonvulsants are now available. The blood level required to control the patient (110-125 mg. percent) is very high and at somewhat higher levels bromide psychosis, neurological disturbances, dermatitis and other signs of bromide intoxication appear (Goodman and Gilman, 1955).

Barbiturates

Phenobarbitone. Since its introduction by Hauptman in 1912 and until the discovery of diphenylhydantoin in 1937, phenobarbitone has been the chief drug for epilepsy. Its main usefulness is in grand mal; petit mal is only occasionally benefitted and psychic seizures are usually exacerbated (Goodman et al., 1949). It it also of value in control of convulsions in tetanus, eclampsia, status epilepticus and cerebral hemorrhage and those caused by cocaine, strychnine, picrotoxin and general anaesthetics. Fingl et al. (1952) have observed that it prevents the cortisone induced lowering of electroshock threshold and may be useful in the management of convulsions during cortisone therapy. Phenobarbitone has definite advantages in that it is the least toxic antiepileptic, it can control status epilepticus also, it is inexpensive, it can be used without the necessity of periodic physical and laboratory examinations and chronic medication causes no deterioration of intellectual powers of the patient. The principal limitation upon its use is its sedative property—for long considered to be a pre-requisite for anticonvulsant action. Another disadvantage, not peculiar to this drug alone, is the exacerbation or even appearance de novo of seizures on abrupt withdrawl of the drug following its prolonged administration (Hauptman, 1912; and Kalinowsky, 1942).

Keller and Fulton (1931) have found that it is the only barbiturate capable of completely abolishing the electrical excitability of motor cortex in monkeys. In sedative doses it is the most effective barbiturate in preventing electroshock seizures in cats (Merritt and Putnam, 1938). Comparison with other antiepileptics, by a variety of laboratory procedures and in psychiatric patients receiving electroshock convulsions (Barany and Stein-Jensen, 1946; Brown et al., 1953 ; Swinyard et al., 1952; Toman et al., 1946, 47) indicates that it is one of the most potent anticonvulsants, that it has a broad spectrum of activity in preventing electroshock and chemoshock seizures and in modifying supramaximal seizure pattern, and that it has a satisfactory therapeutic index and duration of action.

Fairly detailed information is available regarding the neural effects of phenobarbitone (Eccles, 1946; Heinbecker and Bartley, 1940; Marshall, 1941). The barbiturates probably exert their various central nervous system effects by increasing threshold and prolonging recovery time of neurones and these actions may be related to the known ability of barbiturates to depress oxidative metabolism of brain tissue (Goodman et al., 1949). The exact mechanism of anticonvulsant action of these drugs is however still unknown.

The average adult requirement for grand mal cases is 0.1—0.2 gm. daily in divided doses. If phenobarbitone alone is not successful, combination of the drug with diphenylhydantoin should be tried. If heavy doses of phenobarbitone are required some of the untoward effects may be dissipated by the concommitant administration of drugs like amphetamine or dexedrine. The common side effects of the drug include drowsiness, dizziness, ataxia, vertigo, erythematous and urticarial rashes etc. which are seldom severe enough to warrant discontinuance of the therapy.

Mephobarbital (Mebaral). This N-methyl derivative of phenobarbitone was first reported as an anticonvulsant by Heyde and Blum in 1932 and later pharmacological studies have shown its superior safety margin (Swinyard, 1949; Toman et al., 1947; Weese, 1932). It is demethylated to phenobarbitone in the liver, it has the same spectrum of activity and apparently affords the same results as phenobarbitone (Goodman et al., 1949), but it causes less drowsiness (Brown and Smith, 1953; Cohen and Myerson, 1942; Smith 1953). The dosage employed is about twice that of phenobarbitone. Both experimental and clinical trials have shown better results with the combined use of mephobarbital and diphenylhydantoin than with either drug alone (Weaver et al., 1954; and Cohen and Meyerson, 1942; Kaufman, 1950; Kehmer, 1949; Meller and Resch, 1949; Reder, 1954 and others).

Metharbital (Gemonil). It is the N-methyl congener of barbital and is demethylated largely in the liver. The drug is more effective against chemical than against electrical seizures. It is less sedative than other barbiturates (Goodman and Gilman, 1955). It is specially valuable in myoclonic seizures and in patients refractory to therapy with other drugs (Goodman and Gilman, 1955). It is also effective in certain cases of grand mal, pyknoepileptic and mixed seizures. Perlstein (1950) states that it is more effective in seizures caused by organic brain disease. The usual adult dose is 0.1 gm. three times daily.

Among other anticonvulsant barbiturates a mention may be made of 5-ethyl, 5-(1-methyl-1-butenyl) barbituric acid (Davidoff and Doolittle, 1944), Trimethyl barbituric acid, 1-methyl-5-methyl-5-ethyl-barbituric acid (Everett and Richards, 1945; Everett, 1946), spirocyclopentane barbituric acid and spiro-3-ethyl-cyclopentane barbituric acid (Swinyard et al., 1951).

Hydantoin Derivatives

Diphenylhydantoin (Dilantin, Phenytoin, Epanutin). In 1923 Dox and Thomas reported on a large series of compounds including 5,5-diphenylhydantoin which had little or no hypnotic action. In 1937 Putnam and Merrit noted that amongst compounds possessing good anticonvulsant and least hypnotic effects this compound stood out prominently. They presented their clinical experience before the annual meeting of the American Medical Association at San Francisco in June 1938 and thus began, "the third or modern era in therapeutics of epilepsy" (Cohen et al., 1940). Other investigators promptly verified the clinical value of diphenylhydantoin (Felterman 1940; Lenox, 1945 ; Ross and Jackson, 1940 ; Lenox, 1940 etc.) and detailed pharmacological investigations were soon carried out (Gruhzit, 1939 ; Gruber et al., 1940 ; Haury and Drake 1940). The drug is now accepted to be at least equal to phenobarbital in the therapy of grand mal (Lenox, 1946) and an effective agent in some cases of psychomotor epilepsy (Gibbs, 1947; Lenox, 1946), relative behaviour disorders (Freyhan, 1945), and symptomatic epilepsies (Moore, 1946). Its successful use has established the important fact that an antiepileptic drug need not be a hypnotic (Toman and Goodman, 1948). The effects of overdosage of the diphenylhydantoin both in animals (Gruber et al., loc. cit. ; Knoefel and Lehman, 1942) and in man (Aring and Rosenbaum, 1941; Finkleman and Arieff, 1942; Merrit and Putnam, 1939) are excitatory rather than depressant.

The initial laboratory test employed in the discovery of the drug was a seizure threshold test (Putnam and Merritt, 1937) but Utah group of workers have failed to observe any raising of the threshold (Goodman et al., 1946 a & b; Toman et al., 1946), unless the drug is given for a prolonged period (Woodbury, 1952 ; Fingl et al., 1952) or the threshold is lowered by hydration. The most outstanding effect of the drug is modification of pattern of maximal seizures in animals and man (Barany and Stein Jensen, 1946 ; Toman et al., 1946). The change in the seizure pattern has been attributed to a greater action of the drug upon subcortical mechanism than upon the cerebral cortex (Barany and Stein Jensen, 1940). Goodman et al. (1949) however believe that tho drug reduces seizure activity at all levels of the brain and not at any spccific anatomic segment. In large doses the drug has been found to reduce experimentally produced ventricular ectopic activity in dogs (Harris and Kokernot, 1950) and possibly the mechanism of action on heart muscle and nervous tissue may be basically similar.

In many cases it can be beneficially combined with other drugs for controlling seizures. The drugs whose combination with diphenylhydantoin has been experimentally or clinically found beneficial include : phenobarbitone (Chen et al., 1940 ; Fetterman, 1940 ; Huse, 1950 ; Lenox, 1940 ; Robinson and Osgood, 1940 ; Symonds, 1950; Yahr, 1952 and others) ; mebaral (loc. cit.) ; phenurone (Goodman and Gilman, 1955); β–diethyl- aminoethyl-diphenylpropyl acetate—S. K. F. 525 A—(Swinyard et al., 1954) ; chlorpromazine (Bert-

and et al., 1954, 1955; Gujral et al., 1956) and pentamethonium (Bertrand et al., 1955). The most impressive results have been obtained with phenobarbital.

The toxic symptoms commonly encountered during diphenylhydantoin therapy include : a peculiar hyperplasia of the gums which is only of cosmetic importance, neurological symptoms like giddiness, ataxia, tremors, nystagmus, head nodding, diplopia and other ocular disturbances, slurring speech and sometimes delirious hallucinations and other psychotic manifestations ; gastro-intestinal disturbances like acute gastric upsets and rarely haematemesis ; dermatitis usually erythematous, scarlatiniform or morbilliform and rarely liver damage and megaloblastic anaemia (Fetterman, 1950; Goodman and Gilman 1955, Merritt and Putnam, 1938; Ryan and Forsaw, 1956). Attempts have been made to find out if the hyperplasia of gums is due to effect of the drug on the utilisation of ascorbic acid but the reports are conflicting (Drake et al., 1941 ; Emmet et al., 1943 ; Frankell, 1940 ; Gruhzit, 1939 ; Kimball, 1939 ; Merrit and Foster, 1940) and the exact cause in unknown.

The adult daily dose of the drug is 0.2-0.6 gm. The drug is also of value in the treatment of disturbed non-epileptic psychotic patients, problem children, chorea, parkinson's disease and dementia paralytica.

Mesantoin. Mesantoin is the hydantoin analog of mebaral. Clinical use of the drug was suggested by the pharmacological studies of Tainter et al. (1943) and the Utah group of workers Toman and Goodman, 1948, (Goodman et al., 1948 ; Swinward, 1949) who have shown its high activity in raising the threshold against electrical and to a lesser extent against metrazol seizures. It can also modify the pattern of maximal seizures. Clinical trials (Carter and Merritt, 1950 ; Kezol, 1950 ; Loscalzo, 1945, 1947, 1948, 1952 ; Merrit and Carter, 1950 ; Myers, 1948 ; Peterman, 1948 ; Tudor, 1948) show that it can control cases of grand mal and psychomotor seizures refractory to diphenyl-hydantoin and other drugs. Merburg and Helford (1946) have obtained good results in petit mal seizures also. It produces sedation and skin rashes more frequently (Kezol, 1950; Myers, 1948; Loscalzo, 1952 etc.) than diphenyl-hydantoin but gum hyperplasia has not been reported. Cases of liver damage (Kaufman, 1950) and blood dyscrasias (Aird, 1948 ; Best and Paul, 1950; Bloom, 1948) ; have also been reported and enjoin caution for the use of the drug. In some cases it may be better able to control seizures in combination with phenobarbitone (Kezol, 1950 ; Myers, 1948), diphenylhydantoin (Kezol, 1946 ; 1950 ; Myers, 1948) or β-diethylaminoethyldiphenyl propyl acetate (Swinyard et al., 1954). The daily dose of the drug is 0.4-0.6 gm.

Thiantoin. Peterman (1948 b) has found thiantoin superior to diphenyhs hydantoin in grand mal and petit mal. Toman and Goodman (1948) have found that it resembles diphenylhydantoin but there is no hyperplasia of gums. Further studies on the drug are required before it can be consi-dered for routine use.

Other Hydantoins. Many other hydantoin derivatives have been tested for their anticonvulsant activity. 5,5 diphenylene hydantoin has been shown effective against experimental seizures by Knoefel and Lehman (1942) and clinically by Fabing et al. (1947). It does not cause gingival hyperplasia. Lusting and Pensch (1954) have found 5-methyl-5-(3-phenanthryl) hydantoin (Bagosin) quite promising both in experimental and clinical trials. Goodman et al. (1954) and Wilfon et al. (1956) have investigated the anticonvulsant properties of 5,5-diphenyl-tetrahydroglyoxaline-4-one (S.K.F. 2599), tho Mysoline analogue of diphenylhydantoin. Its properties are similar to diphenylhydantoin but the anticonvulsant activity and toxicity is less and hence margin of safety is more. In human beings effective doses produce mild transient nausea and drowsiness.

Oxozolidin-2-4 Diones

Trimethadione (*Tridione*). The drug was synthesised by Spielman in 1944 during a systematic research for new analgesic drugs, and its anticonvulsant properties investigated by Richards and Everett (1944, 1946) and Everett and Richards (1944). The first clinical reports appeared in 1945 (Richards and Perlstein) and since then its highly specific salutory effect in the petit mal triad has been demonstrated by many observers (Lenox, 1941, 1947; Perlstein and Andelman, 1946). Some cases of petit mal seizures may be exacerbrated during the first few days of therapy. The drug is unique in its specificity for spike-wave cerebral dysrhythmia characteristic of petit mal and the E.E.G. frequently reverts to normal. It has also been reported to be useful in some cases of grand mal and psychomotor seizures specially when combined with diphenylhydantoin (Dejong, 1946). It possesses mild but clinically useful analgesic properties (Richards et al., 1946) and may be useful in cerebral palsies (Perlstein and Adelman, 1946).

The outstanding property of the drug is the protection it affords against metrazol induced seizures. To a lesser extent it antagonises convulsions caused by thujone, picrotoxin, procaine and cocaine (Everett and Richards, 1944) and elevates threshold for electroshock in normal and hydrated animals (Swinyard, 1949). It is weaker than other drugs in modifying clinical and experimental seizure pattern and in preventing repetetive firing in a peripheral nerve (Goodman et al., 1949).

Treatment with trimethadione entails the assumption of a certain risk which must be weighed against the benefit to the patient, The toxic signs have been reviewed by Lenox (1947). Hemeralopia (glare phenomenon), the most frequent side effect, is believed to depend upon the retinal effects of the drug. Coloured glasses are often helpful. Rashes which usually disappear on reducing the dose are frequent. Both liver and kidney are important in excretion of the drug and hepatic or renal damage entails caution in the use of the drug. Rarely nephrotic syndrome has been reported. The most serious side effect of the drug is the bone marrow depression leading to blood dyscrasias specially to aplastic anaemia or agranulocytosis. Hence regular

haematological investigations must be carried out during trimethadione therapy and it should not be used with mesantoin.

The dose of the drug is 0.15-0.3 gm. thrice daily. Sudden withdrawl of the drug may worsen the condition of the patient and hence the dose is progressively tapered off. The drug is completely demethylated to 5,5-dimethyl-2,4-oxazolidine in the liver (Butler, 1953).

Paradione. Paradione was snythesised by Spielman (1944) and the anticonvulsant properties were investigated by Everett (1946), and Swinyard (1949) who reported high antimetrazol potency and clinical effectiveness against petit mal. In petit mal occasionally its combination with trimethadione gives better results than does either drug alone. It also benefits some patients of grand mal or psychomotor seizures when used with diphenylhydantoin (Goodman and Gilman, 1955). Side effects are similar to trimethadione but glare phenomenon, the most frequent and most troublesome reaction to trimethadione, is infrequent. Though its anticonvulsant spectrum is similar to trimethadione, its potency against various experimentally induced seizures in laboratory animals is greater (Brown et al., 1952, Swinyard et al., 1952). It is converted into 5-ethyl-5-methyl-2,4-oxazolidine dione in the liver (Butler, 1955) and excreted by the kidney (Swinyard et al., 1952). The total daily dose is 0.9-3.0 gm.

Other Congeners of Trimethadione. Epidon is clinically effective in grand mal but not in petit mal and its anticonvulsant properties in laboratory animals resemble those of diphenylhydantoin (Swinyard, 1949). Malidon another congener of trimethadione, is effective in petit mal and does not produce hemeralopia. The drugs require a detailed study.

Phenurone

Out of a number of substituted acetylurea derivatives synthesised by Spielman et al. (1948), phenylacetylurea (Phenurone) was found to have outstanding anticonvulsant properties in animals (Everett, 1949, Everett and Richards, 1952; Swinyard, 1949). Extensive clinical trials (Gibbs et al., 1949; Tyler and King, 1951) have shown the value of Phenurone in the treatment of psychomotor epilepsy and in refractory cases of grand mal and petit mal (Swinyard and Toman, 1950; Tyler and King, 1951). The drug has had encouraging preliminary trials in the therapy of narcolepsy and cataplexy (Goodman and Gilman, 1955). It acts better in combination with phenobarbitone, diphenylhydantoin or trimethadione (Tyler and King, 1951).

It has a broad spectrum of activity in experimental animals. It is able to raise the threshold for psychomotor seizures and minimal electroshock seizures in normal and hydrated animals, to modify the pattern of maximal electroshock seizures and to raise the threshold for metrazol, strychnine and thujone convulsions (Brown et al., 1953 ; Everett and Richards, 1952; Goodman et al., 1949; Swinyard, 1949). The drug is chiefly degraded into the liver (Weaver et al., 1952).

The common side effects are personality disturbances and gastrointestinal upsets (Tyler and King, 1951). Rare but serious side effects are severe hepatic damage and blood dyscrasias (Everett and Richards, 1952). Milder side effects include insomnia, fatigue, dizziness, insenstivity to pain, skin rashes etc. (Tyler and King, 1951). The average daily dose is 2-3 gms.

Methyl Phenyl Succinimide (Milontin)

A series of *a*-phenyl succinimide derivatives synthesised by Miller and Long (1951) were screened for anticonvulsant activity and Milontin was found especially effective against metrazol seizures (Chen et al., 1951; Zimmerman, 1951). Its spectrum resembles trimethadione and clinical trials have shown it to be specially effective against petit mal seizures (Millichap, 1952; Zimmerman, 1951). Some cases of psychomotor and mixed seizures are also benefitted. Chen and Ensor (1953) have found better results by combining it with diphenylhydantoin and phenobarbitone.

Little is known about its other actions on the nervous system. Most of the drug is degraded within 24 hours and is excreted in urine and bile. The toxic symptoms include nausea, dizziness, drowsiness etc. Millichap (1952) and Millichap and Kirman (1953) haye found transient signs of glomerulotubular damage in high percentage of cases (50 percent). The furture of this drug will be watched with interest.

Amides

Atrolactamide (*Themison*). The anticonvulsant properties of this drug in experimental animals have suggested it as a potential wide spectrum antiepileptic (Jenny et al., 1952). It also exbibits myanesin like depressant properties on various polysynaptic pathways in cerebrospinal axis. The compound is useful in various types of epilepsy particularly grand mal, psychomotor and Jacksonian seizures (Stamps et al., 1952). The drug is rapidly absorbed when given orally and 60-70 percent is excreted unchanged in urine (Abdulian and Sherrod, 1955; Sherrod and Zubaidi, (1953). The average daily dose is 4 gm. and side effects include drowsiness, skin rash, ataxia, and leucopenia.

Hibicon. The compound has been synthesised by Kushner et al. (1951) and its anticonvulsant properties investigated by Harned et al. (1953). They have found it effective against both chemical and electrical seizures. It is more potent and less toxic than diphenylhydantoin. In preliminary clinical trials the drug was found to be useful in grandmal and psychomotor seizures but ineffective in petit mal seizures (Hawkes, 1952). The daily dose is 4-8 gm. The drug is probably metabolised in liver and kidney. Side effects include dizziness, nervousness, gastric disturbances and tremulousness. Mixed seizures respond better when the drug is given with a barbiturate specially Mebaral (Hawkes, 1952).

Mysoline (Primidone)

Mysoline is a new anticonvulsant drug synthesised in 1949 by Bogue and Carrington. It has been experimentally evaluated by Bogue and Carrington (1952) and Goodman et al. (1953). They have found the drug less potent than phenobarbitone by a variety of assay procedures except by the supra maximal electroshock seizure test. The drug has a very low neurotoxicity and a high protective index. Goodman et al. (1953) have drawn attention to the crystalluria obtained after moderate doses in rats and mice but Bogue and Carrington (1952) say that it does not occur in human beings. The potency of the drug is increased by nephrectomy. Liver damage also increases the potency and duration of action (Swinyard et al., 1954). Probably liver and kidney both are important in its degradation and elimination.

The first clinical trials with the drug were carried out by Handley and Stewart (1952) who found it specially effective in grand mal seizures. A large number of reports about its usefulness in various forms of epilepsy have been published in the last three years (Bonkalo and Arthurs, 1953; Butler, 1953; Davis, 1953; Delay et al. 1954; Doyle and Livingston, 1953; Forters, 1953; Nathan, 1954; Smith and McNaughton, 1953; Whitty, 1953). These observers have also reported benefit in a number of cases of psychomotor and petit mal epilepsy. Side effects include nausea, vomitting, vertigo, drowsiness, elation, dysarthria, ataxia, skin rash and rarely pitting edema of the feet. The daily dose is 0.5-1.5 gm.

Gujral and Dhawan (1957) have investigated the effect of diphenylhydantoin, phenobarbitone, trimethadione, Milontin and QZ-2 (Gujral et al., 1957) on the anticonvulsant potency of Mysoline in animals. They find that its action is markedly potentiated by diphenylhydantoin in supramaximal electroshock seizure pattern test particularly when diphenylhydantoin is the major component by weight. In metrazol threshold test maximal potentiation is caused by trimethadione. Clinically synerngistic effect have been reported in grand mal seizures by combining it with diphenylhydantoin (Bonkalo and Arthurs, 1953; Butler, 1953; Forters, 1953; Melin and Waller, 1955; Pence, 1954, Selby, 1953; Smith and McNaughton, 1953; Jimberlake et al., 1955), and phenobarbitone (Calanan and Borelli, 1953); in petit mal seizures by combining with phenobarbitone (Smith and McNaughton, 1953; Selby, 1953) and trimethadione (Selby, 1953); and in psychomotor or mixed seizures by combining it with phenobarbitone (Selby, 1953). However, mysoline is a new compound and its therapeutic status and toxic potentialities will be known fully only after more extensive experimental studies and clinical trials.

Other Drugs Used in Epilepsy

Unsaturated Carbinols. The anticonvulsant properties of a number of unsaturated carbinols have been studied by Margolin et al. (1951), Pan et al. (1952) and Swinyard et al. (1953). Peculiarly enough these compounds cannot raise the threshold of hydrated rats. They can alter seizure pattern

in patients receiving electroshock therapy. Methylparafynol (Dormison) is the most active and least toxic of these compounds. It has been found to potentiate the activity of phenobarbiatal (Brodie et al., 1955). The clinical status of the drug is yet to be established.

Diamox. Begining with starvation 35 years ago, acidifying and dehydrating measures have stood the test of time. Acid ash and ketogenic diets, ingestion of acids and acid forming salts, inhalation of CO_2, restriction of fluids, assisted or not by the addition of cation exchange resins have shown a certain degree of success. Some of the sulfonamides have long been known to inhibit carbonic anydrase and produce acidosis (Mann and Keilin, 1940). Diamox (acetazolamide) is a nontoxic sulphonamide which is a powerful inhibitor of carbonic anhydrase. In contrast to other measures it is easy to administer, has a wider safety margin and a sustained effect.

Millichap et al. (1955) have shown that it prevents electrically induced seizures in mice. The potency seems related to carbonic anhydrase inhibition and not to the production of acidosis. Inhibition of the enzyme leads to accumulation of CO_2 at nerve cell membrane, and resulting decrease of velocity may be responsible for anticonvulsant action (Lancet 1956). Preliminary clinical trials (Ansell and Clarke, 1956; Bergstrom et al., 1952. Lombrosso et al., 1956) show that it may be of value in grand mal of moderate severity, and in some cases of petit mal and mixed idiopathic epilepsy. Side effects include paraesthesia of hand and feet, excessive drowsiness, and increased irritability. Doses upto 200 mg./kg. may be required although lower doses suffice in most cases (Ansell and Clarke, 1956).

Glutamic Acid. Putnam and Merritt (1941) suggested that many anticonvulsants produced an acid millieu within or about the nerve cells in petit mal epilepsy. Price et al. (1943) have suggested the use of d-l or l-glutamic acid because it is intimately related to brain metabolism and is the only amino acid known to be metabolised by the brain tissue (Well-Malherbe, 1936). They have found that petit mal and psychomotor seizures are decreased but there is no relief in grand mal which may be actually worsened. Mental and physical alertness is increased. The amino acid is however ineffective by the laboratory assay methods and thus differs from other anticonvulsants (Goodman et al., 1946). The dose recommendcd is 7-10 gm. and more work is required to judge its correct state.

Quinazolone derivatives. A series of 2, 3 disubstitued quinazolones were synthesized in this laboratory as potential analgesics. Initial screening has shown that some of them are potent hypnotics (Gujral et al., 1956). Three of these compounds QZ-1, QZ-2 and QZ-4 have also been found to be potent anticonvulsant agents in raising the threshold for metrazol convulsions as well as in modifying the supramzximal seizures (Gujral et al., 1957) A detailed laboratory investigation of other neuropharmacological properties of these compounds is being conducted (Kohli, 1957) and their progress will be watched with interest.

Analeptic Sympathomimetic Amines Benzedrine, Dexedrine and Ephedrine have been emplyed in treatment of some cases of petit mal (Goodman et al., 1949), and with phenobarbital to lessen its sedative effects (vide supra). These drugs can raise the convulsive threshold (Tainter et al., 1943) to metrazol shock. Alexander and Weaver (1955), however, found that amphetamine has no anticonvulsant properties against electrical and chemical seizures nor did it alter the anticonvulsant potency of phenobarbitone although clinically the anticonvulsant action of phenobarbitone is enhanced.

Other drugs employed in the treatment of epilepsy including cortical steroids (Mc Quarrie, 1942) ; CO_2 inhalations (Toman and Goodman, 1948) and ketone derivatives (Slater et al., 1952) do not appear established enough to warrant detailed description.

Measures other than drugs

Sociopsychological Measures. It is impossible to treat seizures without treating the person who has them and the environment in which he lives. The epileptic like other people, is a member of numerous groups—family, community, school, trade or business profession, nation etc. and his position in most of these is severely threatened by his disease. This tends to make the epileptic withdraw and build a wall of protection around hismself and he is apt to become self centered and hesistant to plunge into relations with others. Hence his intellectual resources should be utilised and his usefulness in society should be demonstrated, particularly to the patient himself. Often, emotional problems, which are obviously the result of the change in his relations resulting from his disease, loom large in the total clinical picture presented by the epileptic and in many cases the seizures can be seen as a pattern of reaction to emotional stress (Kaufman, 1950). It is necessary to give psychotherapy to such patients. This may involve only superficial measures, such as reassurance or explanation or it may require more intensive treatment, including psychoanalysis. Such treatment is difficult but it is frequently necessary and often enough rewarding to make it worthwhile.

Surgical Measures. Surgical treatment has been advocated in cases in which medical treatment, after a conscientious trial, has failed. This is specially beneficial in cases of focal seizures and consists in removal of the epileptogenic focus by subpial resection (Penfield, 1941; Walker, 1949). The focus must be small in size with no evidence of wide spread brain disease and the patient relatively intact intellectually and emotionally. In cases of psychomotor epilepsy good results have been obtained by temporal lobectomy (Baily and Gobbs, 1951; Green et al., 1951) a procedure not yet universally adopted. As a last resort cortical ablation is a useful procedure in selected cases (Kaufman, 1950).

Dietary and Physical Measures. All epileptics should eat a normal diet with liberal amounts of essential elements but it is advisable to eliminate alcoholic beverages and restrict fluids. Dehydration regimes (Fay, 1930) and

ketogenic diets (Wilder, 1921) are not favoured because of technical difficulties. Whenever possible food substances producing alkalosis should be decreased and replaced by a diet that produces acidosis.

Recently poor cerebral circulation due to inadequate blood flow and oxygenation is also receiving attention as etiological factor for the causation of convulsions. Breathing excercises are encouraged. Improvement of general circulation and accumulation of lactic acid are advantages that far outweigh the small statistical probability of bringing about a seizure owing to over-breathing (Bercel, 1952).

Management of Status Epilepticus and Refractory Cases

Status epilepticus is a medical emergency. The seizures must be brought under control rapidly or the patient will die from exhaustion and inanition. The best measures are the use of intravenous sodium phenobarbital (0·13-0.39 gm.) or ether drip (Kaufman, 1950). Other drugs of value include amobarbital sodium, vinibarbital sodium, paraldehyde and tridione given intravenously (Bercel, 1952). Dilantin can also be given with fluid, electrolytes and nutrients by a stomach tube. Recently Bernhard et al., (1955) have found that 0·6-6 mg./kg. Xylocaine given as 0.1-2 per cent drip in normal saline gives good results and it can also potentiate the action of barbiturates.

In refractory cases sometimes heroic measures are needed, and one has to diverge from the beaten track. Thus introduction of gas in subarachnoid space helps in some cases of petit mal. Electric convulsive treatment which raises the convulsive threshold after each seizure has been used not only with impunity but with success when every thing else has failed (Bercel, 1952). Putnam et al. (1952) advocate hyperintensive treatment with either continued barbital narcosis or with toxic doses of whole battery of anticonvulsants given on successive days. The underlying philosophy of these special measures is the same : one's ingenuity should never concede defeat to epilepsy.

BIBLIOGRAPHY

1. Abdulian, D. H. & Sherrod, T. R. (1955) : *J. Pharmacol. & Exper. Therap.*, **113** : 439.
2. Adrian, E. D. & Moruzzi, G. (1939) : *J. Physiol.*, **97** : 153.
3. Aird, R. B. (1939) : *Arch. Neurol. & Psychiat.*, **42** : 700.
4. Aird, R. B. (1944) : *J. Nerv. & Ment. Dis.*, **99** : 501.
5. Aird, R. B. (1948) : *California Med.*, **68** : 141. (Quoted from 205).
6. Aird, R. B., & Strait, L. (1951) : *J. Pharmacol. & Exp. Therap.*, **103** : 136.
7. Albertoni, P. (1882) : *Arch. f. Exper. Path. u. Pharmakol.*, **15** : 248. (Quoted from 10).
8. Albertoni, W. M., & Weaver, L. C. (1955) : *Arch. int. Pharmacodyn.*, **100** : 472.
9. Algeri, E. J., & Macbay, A. J. (1956) : *Science*, **123** : 183.
10. Alles, G. A., Ellis, C. H., Feigen, G. A. & Redman, M. A. (1947) : *J. Pharmacol. & Exp. Therap.*, **89** : 356.
11. Anderson, H. H. & P'an, S. Y. (1941) : *Proc. Soc. Exp. Biol. Med.*, **46** : 611. (Quoted from Chem. Abs. **35**, 4491, 1941).
12. Anguiano, G., & McIlwain, H. (1951) : *Brit. J. Pharmacol.*, **6** : 448.
13. Ansell, B. A. & Clarke, E. (1956) : *Brit. Med. Jour.*, **4968** : 650.
14. Aring, C. D., & Rosenbaum, M. (1941) : *Arch. Neurol. & Psychiat* **45** : 265.

15. Baglioni, S. & Magnini, M. (1909) : *Arch. Fisiol.*, **6** : 240. (Quoted from 327).
16. Bailley, P. & Gibbs, F. A. (1951) : *J. Am. M. A.*, **145** : 365.
17. Barany, E. H. (1947) : *Arch. int. Pharmacodyn.*, **74** : 155.
18. Barany, E. H. & Stein-Jensen, E. (1946) : *Arch. int. Pharmacodyn.*, **73** : 1.
19. Barlow, R. B. : *Introduction to Chemical Pharmacology*, P122,69, *London, Methuen & Co.*,1955.
20. Belford, J. & Bonnycastle, D. D. (1950) : *J. Pharmacol. & Exp. Therap.*, **99** : 325.
21. Bercel, N. A. (1952) : *J. Am. M. A.*. **149** : 1361.
22. Berger, F. M. (1951) : *Proc. Soc. Exper. Biol. & Med.*, **78** : 277.
23. Berger, F. M. (1952) : *J. Pharmacol. & Exp. Therap.*, **104** : 229.
24. Berger, F. M. & Ludwig, B. J. (1950) : *J. Pharmacol. & Exp. Therap.*, **100** : 27.
25. Berger F.M., Hendley, C.D., Ludwing, B. J., Lynes, T.E.(1956) : *J. Pharmacol. & Exp. Therap.*, **116** : 337.
26. Berger, H. (1929) : *Arch. f. Psychiat*, **87** : 527. (Quoted from 32I).
27. Bergstrom, W. H., Carzoli, R. F., Lombroso, C., Davidson, D. & Wallace, W. M. (1952) : *Am. J. Dis. Children.*, **84** : 771.
28. Bernhard, C. G., Bohm, E. & Hojeheng, S. (1955) : *A. M. A. Arch. Neurol. & Psychiat.*, **174** : 208.
29. Bertrand, I., Gayet-Hallion, Th. & Quivy, D. (1955) : *Arch. int. Pharmacodyn.*, **106** : 283.
30. Bertrand, I., Quivy, D., & Gayet Hallion, Th. (1954) : *C. R. Soc. Biol.*, **148** : 1170, (Abstr. no. 3924, Excerpta Medica Vol. 8, 1954).
31. Best, W. R. & Paul J. T. (1950) : *Am. J. Med.*, **8** : 124. (Quoted from 205).
32. Bianchi, C. (1956) : *Brit. J. Pharmacol.* **11** : 141.
33. Bikeles, C. & Zbyszewski, L. (1914) : *Arch. ges. Physiol.*, **185** : 235. (Quoted from 327).
34. Billman, J. H., Ward, T. G., & Hidy, P. H. (1945) : *J. A. C. S*, **67** : 130. (Quoted from Chem. Abs., **39**, 1407, 1945).
35. Blair, D. (1947) : *Brit. Med. Jour.* **2** : 171.
36. Bliss, C. I. (1935) : *Ann. Applied. Biol.*, **22** : 137.
37. Bloom, N., Lynch, J. P., & Brick, H. (1948) : *J. Am. M. A.*, **138** : 498.
38. Bogue, J. Y. & Carrington, H. C. (1953) : *Brit. J. Pharmacol.*, **8** : 230.
39. Bonkalo, A. & Arthur, R. G. S. (1953) : *Canad. M. J.*, **68** : 570.
40. Borrus, J. C. (1955) : *J. Am. M. A.*, **157** : 1596.
41. Brodie, D. A., Tye, A. & Nelson, J. W. (1955) : *J. Am. Pharm. A*, (Scient. Ed.), **44** : 59.
42. Brown, W. C., Schiffman, D. O., Swinyard, E. A. & Goodman, L. S. (1952) : *J. Pharmacol & Exp. Therap.*, **107** : 273.
43. Brown, W. T. & Smiths J. A. (1953) *South. Med. J.*, **46** : 582,
44. Bubnoff, N. & Heidenhain, R. (1931) : *Pflugers. Arch.*, **26** : 137. (Quoted from I34).
45. Burckhalter, J. H. & Scarborough, H. C. (1955) : *J. Am. Pharm. A.* (Scient. Ed.), **44** : 545.
46. Burger, A. : *Medicinal Chemistry, Vol. I., New York.*, Inter Science Publishers, 1951.
47. Butler, T. C. (1953) : *J. Pharmacol. & Exp. Therap.*, **108** : 11.
48. idem. (1955) : *ibid.*, **113** : 178.
49. idem. (1956) : *ibid.*, **116** : 326.
50. Butler, J. (1952) : *J. Neurol. & Psychiat.*, **57** : 15.
51. Butter, J. M. (1952) : *J. Neurol. Neurosurg. & Psychiat.*, **15** : 37.
52. Bywaters, W. G., Coleman, W. R., Kamm, O. & Merrit, H. H. (1945) : *J. A. C. S.*, **67** : 905. (Quoted from Chem. Abs. **39** : 3282, 1945).
53. Cahen, R. L. (1946) : *J. Pharmacol. & Exp Therap.*, **88** : 343.
54. Calan, W. L. & Borrelli, V. M. (1953) : *Lancet.*, **2** : 42.
55. Canter, S. & Merritt, H. H. (1950) : *Lancet.*, **2** : 103,
56. Cerletli, V. & Bin, L. (1938) : *Arch. Gen. Neurol. Psychiat. & Psychoanalysis*, **19** : 266. (Quoted from I0).
57. Chakravarty, N. K., Woodbury, D. M. & Goodman, L.S. (1956) : *J. Pharmacol. & Exp. Therap.*, **116** : 12.
58. Chen, G., Portman, R., Ensor, C. R. & Bratton, Jr. A. C. (1951) : *J. Pharmacol. & Exp. Therap.*, **103** : 54.
59. Chen, G. & Ensor, C. R. (1953) : *J. Lab. & Clin. Med.*, **41** : 78.

60. Chen, G. & Ensor, C. R. (1954) : *Proc. Soc. Exp. Biol. N. Y.*, **87** : 602.
61. Chen, G. Ensor, C. R. & Portman, R. (1956) : *Arch. int. Pharmacodyn.*, **104** : 333.
62. Chen, G., Portman, R., Ensor, C. R. & Bratton, Jr. A. C. (1951) : *J. Pharmacol & Exp. Therap.* **103** : 54.
63. Cheymol, J. (1950) : *Actualites Pharmacologiques*, **2** : 1.
64. Chu, N., Driver, R. L. & Hanzlik, P. (1948) : *J Pharmacol. & Exp. Therap* , **92** : 291.
65. Cobb, S. Cohen, M. E. & Ney, J. (1938) : *Arch. Neurol. & Psychiat.*, **40** : 1156.
66. Cobb, S Cohen, M. E. (1940) : *Trans, Am. Neurol. Assn.*, **66** : 199.
67. Cohen, B., & Myerson, A. (1942) : *New England J. Med.*, **22** : 336.
68. Cohen, B., Showstack, M. & Myerson, A. (1940) : *J. Am. M. A.*, **114** : 480.
69. Cohen, L. M., & Karn, H. W. (1943) : *J. Comp. Psychol.*, **35** : 307. (Quoted from 70).
70. Corn, M., Lester, M. & Greenberg, L. A. (1955) : *J. Pharmacol. & Exp. Therap.*, **113** : 58.
71. Courvoisier, S. Fournel, J., Ducort, R., Kolsky, M., & Koetschet, P. (1953) : *Arch. int. Pharmacodyn.*, **92**: 305.
72. Darrow, D. C. & Yarnet, H. (1935) : *J. Clin. Invest.* **14** : 266. (Quoted from 312)
73. Davenport, V. A. & Davenport, H. W. (1948): *J. Nutrition*, **36** : 139. (Quoted from 312).
74. Davidoff, E. & Doolittle, G. M. (1944) : *Dis. Ner. System.*, **5** : 84. (Quoted from 327).
75 Davis, J. P. & Lennox, W. G. (1947) : *Proc. A. Research. Nerv. & Ment. Dis* , **36** : 423
75a Idem. (1947) : J. Pediat., **31** : 24.
76. Davis, N. R. (1953) : *Ind. J. Neurol. & Psychiat.*, **4** : 179.
77. De Jong, R. N. (1946) : *J. Am. M. A.*, **103** : 565.
78. De Jong, R. N. (1948) : *Am. Practitioner*, **3** : 233.
79. De Jong, R. N. (1949) : *Am. J. Psychiat.*, **105** : 767.
80. Delay, J., Tenbie, G., Manty, R., Guibert, M. & Persie, J., 1954 : *Therapia.*, **9** : 411.
81. Dercum, F. X. (1919) : *J. Nerv. & Ment. Dis.*, **50** : 168. (Quoted from 327).
82. Domino, E. Peterson, R. J. & Unna, K. R. (1951): *J. Pharmacol. & Exp. Therap.*, **103** : 342.
83. Domino, E. Unna, K. R. & Kerwin, J. (1952) : *Ibid.*, **105** : 486.
84. Dox, A. W. & Thomas, A. (1923) : *J. Am. Chem. Soc.*, **45** : 1811.
85. Doyle, P. J. & Livingston, S. (1953) : *J. Pediat.*, **43** : 413.
86. Drake, M. E., Gruber, C. M., Haury, V. G. & Hart, E. R. (1941) : *J. Pharmacol. & Exp. Therap.*, **71** : 268.
87. idem. ibid. **72** : 383.
88. Dusser De Barenne, J. G. (1933) : *Physiol. Rev.*, **13** : 325.
89. Dusser De Barenne, J. G. & Mc Culloch, W. S. (1939) : *Am. J. Physiol.*, **126** : 482.
90. Eccles, J. C. (1946) : *J. Neurophysiol.*, **9** : 87.
91. Emmet, A. D., Hartzlen, E. R., & Brown, R. A. (1943) : *J. Pharmacol. & Exp. Therap.*, **78** : 215.
92. Erickson, T. C., Gibson, W. E., Elvehyem, C. A. & Newell, G. W. (1947) : *Proc. A. Research. Nerv. & Ment. Dis.*, **26** : 164.
93. Erlenmeyer, H. (1938) . *Helv. Chem. Acta.*, **21** : 1013.
94. Everett, G. M. (1946) : *Federation Proc.*, **5** : 26.
95. Everett, G. M. (1948) : *International League against Epilepsy*, (Quoted from 327).
96. Everett, G. M. (1949) : *Federation Proc.*, **8** : 289. (Quoted from 100).
97. Everett, G. M. & Richards, R. K. (1944) : *J. Pharmacol. & Exp. Therap.*, **81** : 402.
98. idem. (1945) : *Federation Proc.*, **4** : 20.
99. idem. (1950) : *Federation Proc.*, **9** : 270.
100. idem. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 303.
101. Fabing, H. D., Gayle, R. F. & Hawkins, J. R. (1947) : *Proc. A. Research. Nerv. & Ment. Dis.*, **26** : 398. (Quoted from 327).
102. Fay, T. (1930) : *Arch. Neurol. & Psychiat.*, **25** : 920. (Quoted from 177).
103. Fetterman, J. L. (1940) : *J. Am. M. A.*, **114** : 390.
104. Finger, F. W. (1947) : *Psychol. Bull.*, **44** : 201. (Quoted from 70).
105. Fingl, E., Olsen, L. J., Harding, B. W., Cockett, A. T. & Goodman, L. S. (1952) : *J. Pharmacol. & Exp. Therap.*, **105** : 37.
106. Finkelman, I. & Arieff, A. J. (1942) : *J. Am. M. A.*, **118** : 1209.
107. Forda, O. & McIlwain, H. (1953) : *Brit. J. Pharmacol.*, **8** : 225.

108. Forters, R. A. (1953) : *El. Medicp.*, **3** : 28.
109. Frankel, S. I. (1940) : *J. Am. M. A.*, **114** : 1320.
110. Freedman, A. M., Bales, P. D., Willis, A. & Himwich, H. E. (1948) : *Am. J. Physiol.*, **156** : 117.
111. Freyhan, F. A. (1945) : *Arch. Neurol. & Psychiat.*, **53** : 370.
112. Frommel, E., Radouco, C., Gold, P., Greder, G., Melkonian, D., Radouco, S., Strassbergers, L., Vallette, F. & Ducommuns, M. (1952) : *Arch. int. Pharmacodyn.*, **92** : 44.
113. Frost, I. (1939) : *J. Ment. Sc.*, **85** : 976. (Quoted from 327).
114. Funderburk, W. H. & Unna, K. R. (1953) : *J. Pharmacol. & Exp. Therap.* **107** : 344, 356 ; **108** : 94.
115. Garciadiego, J., Chavez, F. N. & Obrador, O. S. (1948) : *Proc. Soc. Exp. Biol. Med.*, **68** : 584.
116. Geyelin, H. R. (1921) : *Med. Record.*, **99** : 1037.
117. Gibbs, E. L. & Gibbs, F. A. (1947) : *Proc. A. Research. Nerv. & Ment. Dis.*, **26** : 366.
118. Gibbs, F. A. (1947) : *Ann. Int. Med.*, **27** : 548. (Quoted from 327).
119. Gibbs, F. A., Everett, G. M. & Richards, R. K. (1949) : *Dis. Nerv. System.*, **110** : 47. (Quoted from 100).
120. Gibbs, F. A., Everett, G. M. & Richards, R. K. (1948) : *Proc. Am. Br. Internat. League Against Epilepsy.* (Quoted from I34).
121. Gold, P., Frommel, E., Radouco, C., Greder, G., Melkonian, D., Della Santa, R., Radonco, S., Valleti, F. & Ducommun, M. (1952) : *Arch. int. Pharmacodyn.*, **91** : 437.
122. Goldstein, H. H. & Weinberg, J. (1940) : *Arch. Neurol. & Psychiat.*, **43** : 453
123. Goodman, L. S. & Gilman, A : *The Pharmacological Basis of Therapeutics, New York, Macmillam & Co*, 1955
124. Goodman, L. S. & Lih, B. (1941) : *J. Pharmacol. & Exp. Therap.* **72** : 18.
125. Goodman, L. S. & Toman, J. E. P. (1948) : *First National Symposium Am. Chem. Soc. Div. Medicinal, Chem.* (Quoted from I34).
126. Goodman, L. S., Gilman, A. & Hart, N. (1943) : *Federation Proc.*, **2** : 80.
127. Goodman, L. S., Swinyard, E. A. & Toman, J. E. P. (1946) : *Arch. Neurol. & Psychiat.*, **56** : 20.
128. Goodman, L. S., Toman, J. E. P. & Swinyard, E. A. (1946) : *Am. J. Med.*, **1** : 213.
129. idem. (1948) : *Proc. Soc. Exp. Biol. & Med.*, **68** : 584.
130. idem. (1949) : *Arch. int. Pharmacodyn.*, **78** : 144.
131. Goodman, L. S., Grewal, M. S., Brown, W. C. & Swinyard, E. A. (1953) : *J. Pharmacol. & Exp. Therap.*, **108** : 168.
132. Goodman. L. S., Swinyard, E. A., Brown, W. C., Schiffman, D. O., Grewal, M. S. & Bliss, E. L. (1953) : *J. Pharmacol. & Exp. Therap.*, **108** : 428.
133. Goodman, L. S., Swinyard, E. A., Brown, W. C. & Schiffman, D. O. (1954) : *J Pharmacol. & Exp. Therap.*, **110** : 403.
134. Goodsell, J. S. (1955) : *Federation Proc.*, **14** : 345.
135. Gowers, W. R. : *Epilepsy & Other Chronic Convulsive Diseases, London*, 1881.
136. Green, J. R., Duisberg, R. E. H. & McGrath, W. B. (1951) : *J. Neurolsurg.*, **8** : 157. (Quoted from 2I).
137. Greenberg, L. A., Lester, D. (1953) : *Quart. J. Stud. Alc.*, **14** : 385. (Quoted from 70).
138. Grewal, M. S., Swinyard, E. A., Jenson, H. V. & Goodman, L. S. (1954) : *J. Pharmacol. & Exp. Therap.*, **112** : 109.
139. idem. (1954) : *Federation Proc.*, **13** : 361.
140. Griffith, W. J. (1942) : *J. Comp. Psychol.*, **33** : 29.
141. idem. (1942) : ibid., **34** : 263.
142. Grinker, J. (1920) : *J. Am. M. A.*, **75** : 588.
143. Gruber, C. M., Haury, V. G. & Drake, M. E. (1940) : *J. Pharmacol. & Exp. Therap.*, **68** : 433.
144. Gruber, C. M. & Kohlstaedt, K. G. Moore, R. B. & Peck, F. B. (1954) : *J. Pharmacol. & Exp. Therap.* **112** : 480.

145. Gruhzit, O. M. (1939) : *Arch. Path.*, **28** : 761.
146. Gujral, M. L., Kohli, R. P. & Saxena, P. N. (1955) : *J. Ass. Phys. Ind.*, **2** : 29.
147. Gujral, M. L., Sareen, K. N. & Kohli, R. P. (1957) : *Ind. J. Med. Res.*, **45** : 2II.
148. Gujral, M. L., Saxena, P. N. & Kulsreshtha, J. K. (1956) : *J. Ind. Med. Prof.*, **3** : 1141.
149. idem (1956) : *J. Ass. Phys. Ind.*, **4** : 451
150. Handley, R. & Stewart, A. S. R. (1952) : *Lancet*, **242** : 742.
151. Haury, V. G. & Drake, M. E. (1940) : *J Pharmacol. & Exp. Therap.*, **68** : 36.
152. Harris, A. S. & Kokernol, R. H. (1950) : *Am. J. Physiol.*, **163** : 505.
153. Harned, B. K., Cunningham, R. W., Clark, M. C., Hine, C. H., Kane, M. M., Smith, Jr. F. H., Vessey, R. E., Yuda, N. N. & Zabransky, F. W. (1953) : *J. Pharmacol. & Exp. Therap.*, **107** : 403.
154. Harris, T. A. B. (1955) : *Lancet*, **268** : 181.
155. Hartelius, (1950) : *Am. J. Psychiat.*, **107** : 95. (Quoted from ref. 46, P 151).
156. Hauptmann, A. (1912) : *Munch. Med. Wchnschr.*, **59** : 1907, (Quoted from 153)
157. Hawkes, C. D. (1952) : *Arch. Neurol. & Physchiat.*, **67** : 815. (Quoted from 153)
158. Hazard, R., Cheymol, J., Chabrier, P. & Swarzewska, K. (1948) : *Therapie*, **3** : 223; C.R. Acad. Paris, 226, 1850.
159. idem. (1949) : *Therapie*, **4** : 276.
160. idem. (1950) : *c. r. Acad. Sci. Paris*, **230** : 243
161. Heinbecker, P. & Bartley, S. H. (1940) : *J. Neurophysiol.*, **3** : 219.
162. Hemphill, R. E. & Walter. W. G. (1941) : *Lancet.*, **248** : 446.
163. Henze, H. R. & Speer, R. J. (1939) : *J. A. C. S.*, **61** : 3376.
164. Henze, H. R. & Magee, J. W; (1940) : *Ibid.*, **62** : 912.
165. Henze, H. R. & Smith, P. E. (1943) : *J. A. C. S.*, **65** : 1090.
166. Henze, H. R. & Nunn, L.G. (1947) : *J. Org. Chem.*, **12** : 543.
167. Henze. H. R. & Leslie. W. B. (1950) : *J. Org. Chem.*, **15** : 991.
168. Heyde, W. (1932) : *Klin. Wchnschr.*, **11** : 1874. (Quoted from 327).
169. Hiatt, E. P. (1939) : *Am. J. Physiol.*, **126** : 533.
170. Huse, A. (1950) : *Birt. M. J.*, **1** : 1436.
171. Jackson, J. H., Selected Writings of John Hughlings Jackson Vol. 1 Edited by James Tayler, London, 1931.
172. Jellinek, S. (1920) : *Med. Klin. (Munich)* **16** : 1126. (Quoted from 327).
173. Jenney, E. H. & Lee, L. D. (1951) : *J. Pharmacol. & Exp. Therap.*, **103** : 349.
174. Jenney, E. H., Lee, L. D., William, H. C. & Pfeiffer, C. C. (1952) : *J. Pharmacol & Exp. Therap.*, **106** : 398.
175. Jenney, E. H. & Pfeiffer, C. C. (1956) : *J. Pharmacol. & Exp. Therap.*, **116** : 33.
176. Kalinowsky, L. B. & Kennedy, F. (1943) : *J. Nerv. & Ment. Dis.*, **98** : 56.
177. Kaufman, I. C. (1950) ; *M. Clin. North. America.*, **34** : 1507.
178. Kaufman. I. C. & Watson, C. W., (1948) : Proc. Empire Electroenceph. Soc., **5**. (Quoted from 327).
179. Kehrer, F. A. (1939) : *Med. Klin.*, **44** : 1211, (Abs. in J. A. M. A. **142** : 375, 1950).
180. Keith, H. M., Essex, H. E. & Schlottharer. C. F. (1944) : *Am. J. Dis. Children.*, **68** : 265.
181. Keller, A. D. & Fulton, J. F. (1931) : *Am. J. Physiol.*, **97** : 537.
182. Kimball, O. P. (1939) : *J. Am. M. A.*, **112** : 1244.
183. Kohli, R. P. (1957) : *Personal Communication.*
184. Kopeloff, N., Baruera, S. F., & Kopeloff, L. M. (1944) : *Am. J. Psychiat.*, **101** : 201.
185. Kozelka, F. L.. Hire, C. H., & Grieler, M. F. (1942) : *Federation Proc.*, **1** : 256.
186. Kozol, H. L. (1946) : *Am. J. Psychiat.*, **103** : 154.
187. idem. (1950) : *Arch. Neurol. & Psychiat.*, **63** : 235.
188. Knoefel, C. K. & Lehman, G. (1942) : *J. Phvrmacol. & Exp. Therap.*, **76** : 194.
189. Kushnar, S., Cassel, R. I., Morton, J. & Williams, J. H. (1951) : *J. Organ. Chem.*, **16** : 1283.
190. Lancet, (1956) : Annotation, **270** : 273,
191. Langecker, H. Sehulman, H.S. & Junkman, K. (1953): *Arch. Exp. Pathol. Pharmacol.*, **219** : 139.

192. Lanphier, E. H. (1949) : *Federatian Proc.*. **8** : 312.
193. idem. : (1949) : *The Quart. J. Phi. Beta. Pi.*, P 136. (Quoted from 246).
194. Lenox, W. G. (1940) : *J. Am. M. A.*, **114** : 1347.
195. idem. : (1945) : *J. Am. M. A.*, **129** : 10369.
196. idem. : (1945) : *M. Clin. North. America.*, **27** : 1114.
197. idem. : (1946) b : Science & Seizures., New York, (1949) : *J. Pediat.*, **29** :356.
198. Lindsley, D. B., Finger, F. W. & Henery, C. E. (1942) : *J. Neurophysiol.*, **5** : 185.
199. idem. : (1947) : *J. Am. M. A.*, **135** : 496.
200. Lockock, C. (1857) : *Lancet.*, **1** : 528, (Quoted from 273).
201. Lombroso, C., Davidson, D. T. & Gross Biarchi, L. (1956) : *J. Am. M. A.*, **166** : 268.
202. Loscalzo, A. E. (1945) : *J. Nerv. & Ment. Dis.*, **101** : 537.
203. idem. : (1947) : *J. Am. M. A.*, **135** : 496.
204. idem. : (1948) : *J. Am. M. A.*, **138** : 1114.
205. idem : (1952) : *Neurology.*, **2** : 403.
206. Lowell, D. J. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 404. (Quoted from 256).
207. Lustig, B., Persch, W. (1954) : *Arzneimittelforsch.*, **4** : 733, (Abstr. No. 422, Excerpta Medica, Pharmacol., Vol. 9, 1956).
208. Luton, F. H., Blalock, J., Baxter, J. H. and Stoughton, R. W. (1941) : *Proc. Soc. Exp. Biol. Med.*, **47** : 245.
209. Mackay, R. P. & Goottstein, W. K. (1948) : *J. Am. M. A.*, **132** : 13.
210. Maier, N. R. F. (1943) : *J. Comp. Psychol..*, **35** : 327.
211. Maier, N. R. F. & Glasser, N. M. (1946) : *J. Comp. Psychol.*, **30** : 413.
212. Mann, T. & Keilin, D. (1940) : *Natnre*, **146** : 164.
213. Manburg, O. & Helfard, M. (1946) : *J. Nerv. Ment. Dis.*, **104** : 465.
214. Margoline, S., Perlman, P., Villani, F. & McGarack, T. H. (1951) : *Science.*, **114** : 384.
215. Marshall, P. G. & Vallance, D. K. (1954) : *J. Parm. Pharmacol.*, **6** : 740.
216. idem. : (1956) : **7** : 404.
217. Marshall, W. H. (1941) : *J. Neurophysiol.*, **4** : 24.
218. McGulloch, W. S. (1947) : *Proc. Fed. Am. Soc. Exp. Biol.*, **6** : 448.
219. McKee, R. L. and Henze H. R. (1944) : *J. A. C. S.*, **66** : 2020.
220. Mc Quarrie, J., Anderson, A. & Zeigler, M. R. (1942) : *J. Clin. Endocinol.*, **2** : 406. (Quoted from 327).
221. Melin, K. A. & Waller, G. (1955) : *Swenska Lakartidn.*, **52** : 387.
222. Meller, R. L. & Resch, J. A. (1949) : *Postgraduate Med.*, **6** : 452.
223. Mercier. J. (1950) : *Comp. rend. Soc. Biol.*, **144** : 1174, 1677, 1711.
224. Merritt, H. H. & Brenner, C. (1947) : *Bull. New York Acad. Med.*, **23** : 292.
225. Merritt, H. H. & Carter, S. (1950) : *Med. Clin. North. America.* **34** : 341.
226. Merritt, H. H. & Foster, (1940) : *Am. J. Med. Sc.*, **200** : 541. (Quoted from 86).
227. Merritt, H. H. & Putman, T. J. (1937) : *Science*, **85** : 525.
228. idem. (1937) : *Trans. Am. Neurol. Assn.*, **63** : 123–28.
229. idem. (1938) : *J. Am. M. A.*, **111** : 1068.
230. idem. (1938) : *Arc. Neurol. & Psychiat.*, **39** : 1003.
231. idem. (1939) : *Arch. Jeurol. & Psychiat.*, **42** : 1053.
232. idem. (1940) : *Am. J. Psychiat.*, **96** : 711.
233. idem. (1940a) : *Trans. Am. Neurol. Assn.*, **66** : 78.
234. idem. (1945a) : *Epilepsia*, **3** : 51.
235. Merritt, H. H., Putman, T. J. & Bywater, W. G. (1945) : *J. Pharmacol. & Exp. Therap.* **84** : 67.
236. idem. (1945) : *Arch. Neurol. & Psychiat.*, **54** : 319.
237. Merritt, H. H., Putman, T. J. & Schwab, O. M. (1938) : *Arch. Neurol. & Psychiat.*, **39** : 1103.
238. Miller, C. A. & Long, L. M. (1951) : *J. Am. Chem. Soc.*, **73** : 4895.
239. Millichap, J. G. (1952) : *Lancet.*, **2** : 907.
240. Millichap, J. G. & Kirman, B. H. (1953) : *Lancet.*, **1** : 1075.
241. Millichap, J. G. & Woodbury, D. M. (1954) : *Am. Soc. Pharmacol. & Exp. Therap.*, Sep. 6—8, 1954. (Quoted from ref. 123, page 867).
242. Millichap, J. G., Woodbury, D. M. & Goodman, L. S. (1955) : *J. Pharmacol. & Exp. Therap.*, **115** : 251.

243. Moore, M. T. (1946) : *Am. J. Surg.*, **72** : 883.
244. Myers, H. J. (1948) : *Med. Ann. of the District of Columbia,* **18** : 449.
245. Nathan. P. W. (1954) : *Lancet,* **1** : 21.
246. Orcult, J. A. & Prytherch, J. P. (1956) : *Arch. int. Pharmacodyn.,* **106** : 60.
247. Osgood, R. & Robinson, L. (1938) : *Arch. Neurol. Psychiat.,* **40** : 1178 (Quoted from Chem. Abs. **33** : 2586, 1939).
248. Pan, S. Y., Gardocki, J. F., Hanfenist, M. & Bavely, A. (1952) : *J. Pharmacol. & Exp. Therap.,* **107** : 459.
249. Pellmont, B., Studer, A. & Jürgens, R. (1955) : *Schweiz, Med. W. Schr.,* **85** : 350.
250. Penfield, W. & Erickson, T. C. (1941) : *Epilepsy & Cerebral Localisation, Springfield.* (Quoted from 177).
251. Penfield, W. & Humpherys, S. (1946) : *Arch. Neurol. & Psychiat.,* **43** : 240.
252. Pence, L.M. (1954) : *Texas State Med. J.,* **50** : 290.
253. Perlstein, M.A. (1950) : *Pediatrics,* **5**: 448.
254. Perlstein, M. A. & Andelman, M. B., (1946) : *J. Pediat,* **29** : 20. (Quoted from 85).
255. Peterman, M. G., (1948) : *South Med. J.,* **41** : 62. (Quoted from 326).
256. Pfeiffer, C. C., : *Neuropharmacology, First Conference,* P. 168, *New York, J. Macy Foundation, 1955..*
257. Pollock, L. J., (1942) : *J. Pharmacol. and Exp. Therap.* **74** : 365.
258. Price, J. C., Waelsch, H. & Patnam, T. J., (1937) : *Science.,* **85** : 525.
259. idem. (1943) : *J. Am. M. A.,* **112** : 1153.
260. Putman, T. J., Bercel, N. A., & Rothenberg, S. (1952) : *Unpublished observation,* (Quoted from 21).
261. Putman, T. J. & Merritt, H.H., 1941a : *Arch Neurol. & Psychiat.,* **45** : 505. (Quoted from 26).
262. Quevauviller, A. & Garcet, S. (1953) : *Therapie,* **8** : 749, (Quoted from Excerpta Medica (Pharmacol). **7** : 1954, Abstr. No. 5434).
263. Radomski, J. L. & Woodland, G. (1949) : *J. Pharmacol. & Exp. Therap.,* **95** : 420.
264. Reder, E. L. (1954) : *New York J. Med.,* **54** : 1659.
265. Richards, R. K. & Everett, G. M. (1944) : *Federation Proc.,* **3** : 39.
266. idem. (1946) : *J. Lab. Clin, Med.,* **31** : 1330.
267. Richards, R. K. & Perlstein, M. A. (1945) : *Abstract in Arch. Neurol. & Psychiat.,* **55** : 164.
268. Robinson, L. J. & Osgood, R, (1940) : *J. Am. M. A.,* **114** : 1334.
269. Ross, A. T. & Jackson, V. (1940 : *Ann. Int. Med.,* **14** : 770.
270. Ronchetti, V. (1940) : *Gazz. Ospedali, Clin.,* **61** : 9: (Quoted from Chem. Abs. **34** : 7412, 1940).
271. Rosa, M. C. (1942) : *Rev. Soc. brasil. quim.,* **11** : 86. (33 references). (Quoted from **38**, 5043, 1944)
272. Ryan, G. M. S. & Forserv, J. W. B. (1955): *Brit. M. J.,* **2** : 242.
273. Salter W. T.: *A Text Boo kof Pharmacology, P, & Publisher Philadelphia,* 1953.
274. Sampson, W. L. & Fernandez, (1939) : *J. Pharmacol. & Expt. Therap.,* **65** : 275.
275. Sandberg, F. (1951) : *Acta. Physiol. Scand.,* **24** : 149.
276. Schaffarzick, R. W. & Brown, B. J. (1952) : *Science,* **116** : 663.
277. Schallak, W., Kuehn, A. & Seppelin, D.K. (1956) : *J. Pharmacol & Exp. Therap.,* **118**, 139.
278. Schiff, E. Z. (1922) : *Ges Expt. Med.,* **28** : 127. (Quoted from 326).
279. Schneider, J. A. (1954) : *Proc. Soc. Expt. Biol. N. Y.,* **87** : 614.
280. Schneider, J. A. & Earl, A. (1954) : *Neurology,* **4** : 657.
281. Selling, L. S. (1955) : *J. Am. M. A.,* **157** : 1594.
282. Shaw, F. H., Simon, S. E., Cass, N. & Shulman, A. 1954 : *Nature,* **174** : 402.
283. Sherington, C. S. (1906) : *The Integrative action of the Nervous System, New Haven, Conn.,* (Quoted from 134).
284. Sherrod, T. R. & Zubaidi, H. I. (1955) : *J. Pharmacol. & Exp. Therap.,* **109** : 148.
285. Shohl, J. (1944) : *J. Comp. Psychol.,* **37** : 243.
286. Shulman, A. (1955) : *Brit. Med. J.,* **1** : 1238.
287. Silver, M. L., Zevin, S. S., Kark, R. E. & Johnson, R. (1947) : *Proc. Soc. Exper. Biol. & Med.,* **66** : 408.

288. Slater, I. H. S., O'Leary, J. F. & Leary, D. E. (1952) : *J. Pharmacol. & Exper. Therap.*, **104** : 168.
289. Smith, J. A. (1953) : *J. Am. M. A.*, **152** : 384.
290. Smith, K. V. (1941) : *J. Camp. Psychol.*, **32** : 311.
291. Smith, B. H. & McNaughton, F. L. (1953) : *Canad. M. A. J.*, **168** : 464.
292. Speransky, A. (1926) : *Ann. Inst. Pasteur.*, **40** : 213. (Quoted from 327).
293. Spiegel, E. A. (1937) : *J. Lab. & Clin. Med.*, **22** : 1274. (Quoted from 10).
294. Spiegal, E. A. & Wycis, H. (1945) : *J. Lab. & Clin. Med.*, **30** : 947.
295. Spielman, M. A. (1944) : *J. Am. Chem. Soc.*, **66** : 1244.
296. Spielman, M. A. & Everett, G. M. (1948) : *J. Am. Chem.* Soc., **70** : 1021.
297. Spratling, W. P. : *Epilepsy and its Treatment, Philadelphia,* (1904). (Quoted from 327).
298. Stamps, F. W. Marshall, W., Orloff, M. J., Gibbs, F. A. & Pfeiffer, C. C. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 418.
299. Stein, F. (1943) : *J. Am. M. A.*, **122** : 268.
300. Stephens, R. R. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 418. (Quoted from 256).
301. Stone, T. T. & Ariff, A. J. (1940) : *Arch. Neurol. & Psychiat.*, **43** : 299.
302. Swanson, E. E., Anderson, R. C. &Gibson, W. R. (1956) : *J. Am. Ph. Ass.*, **45** : 40.
303. Swinyard, E. A. (1949) : *J. Am. Pharm. A.* (Science Ed.), **38** : 201.
304. idem. (1949) : *Am. J. Physiol.*, **156** : 163.
305. Swinyard, E. A. & Goodman, L. S. (1946) : *Federation Proc.*, **5** : 205.
306. Swinyard, E. A. & Toman, J. E. P. (1948) : *Am. J. Physiol.*, **154** : 207.
307. Swinyard, E. A. & Toman, J. E. P. (1950) : *J. Pharmacol. & Exp. Therap.*, **100** : 151.
308. Swinyard, E. A., Bliss, E. L. & Goodman, L. S. (1951) : *J. Pharmacol. & Exp, Therap.*, **103** : 346
309. Swinyard, E. A., Brown, W. C. & Goodman, L. S. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 319.
310. Swinyard, E. A., Madsen, J. A. & Goodman, L. S. (1954) : *J. Pharmacol. & Exp. Therap.*, **111** : 54.
311. Swinyard, E. A., Schiffmann, D. O. & Goodman, L. S. (1952) : *J. Pharmacol. & Exp. Therap.*, **105** : 365.
312. idem. (1955) : *J. Pharmacol. & Exp. Therap.*, **114** : 160.
313. Swinyard, E. A., Weaver, L. C. & Goodman, L. S. (1952) : *J. Pharmacol. & Exp. Therap.*, **104** : 309.
314. Swinyard, E. A., Schiffman, D. O., Brown, W. L., Grewal, M. S. & Goodman, L. S. (1953) : *Arch. Int. Pharmacodyn.*, **94** : 81.
315. Symmonds, L. (1950) : *Brit. M. J., P 1047.*
316. Tainter, M. L., Tainter, E. G., Lawrence, W. S., Neuru, E, N., Lacke, R. W., Ludena, E. P., Kirtland Jr. H. V. & Gouzabs, R.I. (1943) : *J. Pharmacol. & Exp. Therap.*, **79** : 44.
317. Tedeschi, O., Swinyard, E. A. & Goodman, L. S. (1956) : *J. Pharmacol. & Exp. Therap.*, **116** : 107.
318. Tempkin, O.: *The falling sickness ; a history of Epilepsy from the Greeks to the begining of Modern neurology., Baltimore, 1955.* (Quoted from 10).
319. Terry, G. S. : *Fever and Psychosis, New Yark,* (1939)
320. Tiffeneau, M. (1943) : *Chem Zentr.*, **11** : 1894.
321. Timberlake, W. H., Abbot, J. A. & Schwab, R. S. (1955) : *New Engl. J. Med.*, **252** : 304.
322. Timiras, P. S., Woodbury, D. N. & Goodman, L. S. (1954) : *J. Pharmacol. & Exp. Therap.*, **112** : 80.
323. Toman, J. E. P. (1951) : *Neurology*, **1** : 444.
324. Toman, J. E. P. (1952) : *Pharmacol. Rev.*, 4 : 168. (P 192).
325. Toman, J. E. P. : *Neurochemistry by Elliot, Page and Quastel, P 534-37, Springfield,* ILL., *Charles C. Thomas, 1955.*
326. Toman, J. E. P. & Davis, J. P. (1949) : *J. Pharmacol. & Exp. Therap.*, **97** : 425.
327. Toman, J. E. P. & Goodman, L. S. (1948) : *Physiol. Rev.*, **28** : 409.
328. idem. (1947) : *Proc. A. Research. Nerv. & Ment. Dis.*, **26** : 141.
329. Toman, J. E. P. & Taylor, J. D. (1952) : *Epilepsia, 3rd series*, **1** : 31. (Quoted from 123).
330. Toman, J. E. P., Everett, G. M. & Richards, R. K. (1952) : *Texas. Rep. Biol. & Med.*, **10** : 96.

331. Toman, J E. P., Loewe, S. & Goodman, L. S. (1947) : *Arch. Neurol. & Psychiat.*, **58** : 312.
332. Toman, J. E. P., Swinyard, E. A. & Goodman, L. S. (1946) : *J. Neurophysiol.*, **9** : 231.
333. Toman, J. E. P., Evans, W. H., Hanston, S. C., Miller, H. V., Nance, J. M., & Wilson, B. K. (1950) : *Federation Proc.*, **9** : 321.
334. Tripod, J., Bein, H. J. & Meier, R. (1954) : *Arch. int. Pharmacodyn.*, **96** : 406.
335. Tudor, R. B. (1948) : *Lancet*, **68** : 391.
336. Tyler, M. W., & King, E. Q. (1951) : *J. Am. M. A.*, **147** : 17.
337. Walker, A. E. : *Post Traumatic Epilepsy, Springfield, Ill., 1949.* (Quoted from 177).
338. Ware, E. (1950) : *Chem. Rev.*, **46** : 403. (SAR : Page 453-55).
339. Weaver, L. C., Swinyard, E. A. & Goodman, L. S. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 319.
340. idem. (1954) : *J. Pharmacol. & Exp. Therap.*, **110** : 52.
341. Weaver, L. C., Swinyard, E. A., Woodbery, L. A. & Goodman, L. S. (1955) : *J. Pharmacol. & Exp. Therap.*, **113** : 359.
342. Weeks, H. (1932) : *Deutsche Med. Wchnschr.*, **58** : 696. (Quoted from 327).
343. Weit-Malhenbe, H. (1936) : *Biochem. J.*, **36** : 665.
344. Wenzel, D. G. (1955) : *J. Am. Ph. Assn.*, **44** : 550.
345. Wenzel, D. G. & Keplinger, M. B. (1955) : *ibid.*, **44** : 56.
346. Wenzel, D. G. & Koff, G. Y. (1956) : *ibid.*, **45** : 669.
347. Wilder, R. M. (1921) : *Proc. Staff. Meetings Mayo Clinic*, **2** : 307.
348. Wilfon, J. G., Much, E. & Mattis, P. A. (1956) : *J. Pharmacol. & Exp. Therap.*, **116** : 62.
349. Wilks, S. : *Guy's Hospital Reports.*, **12** : 152. 18886 (Quoted from 315).
350. Woodbury, D. M. (1952) : *J. Pharmacol. & Exp. Therap.*, **106** : 425.
351. Wycis, H. T. & Spiegel, E. A. (1945) : *Am. J. Med. Sc.*, **209** : 548. (Quoted from Chem. Abst., **39**: 3066, 1945).
352. idem. (1945) : *J. Lab. Clin. Med.*, **30** : 947. (cf. ref. 294). (Quoted from Chem. Abst., **40**, 952I, 1946).
353. Wyngaarden, J. B., Woods, L, A., Ridley, R. & Seivers, M. H. (1949) : *J. Pharmacol. & Exp. Therap.*, **95** : 322. (Quoted from reference 19, P 71).
354. Yahr. M. D., Sciarra, D., Career, S. & Merritt, H. H. (1952) : *J. Am. M. A.*, **150** : 663.
355. Zimmerman, F. T. (1951) : *Arch. Neurol. & Psychiat.*, **66** : 156.
356. Ziskhid, E., Sjaardema, H. & Ereel, N. A. (1946) : *Science*, **104** : 462.