these groups are those epileptics who can be called "idiopathic," and those patients in whom the brain has been damaged by pathological processes of a diffuse character. The E.E.G.s in these groups show widespread complex discharges affecting both hemispheres, often in a symmetrical manner. The classical bilaterally synchronous 3-per-second spike-and-wave discharge occurring upon a background of normal cortical activity is the type of discharge—it seems at the present time the only type of E.E.G. discharge that can be associated with idiopathic epilepsy. Yet there are rare instances in which even this type of subcortical discharge is secondary to a cortical focus related to a local lesion. This is the case of "secondary subcortical epilepsy" (Case 2: Fig. 3). Three-per-second spike-and-wave discharges occur much more commonly in the E.E.G.s of young epileptics than in those of adult patients, and the meaning of this is not clear. Is idiopathic epilepsy largely a condition of childhood? Since epilepsy, particularly major seizures, can itself very probably damage the brain by anoxia and therefore be itself a cause of further epilepsy, the problem is a difficult one.

Widespread bilateral fast and slow forms of spike-and-wave discharge, episodes in which groups of spikes predominate over slow waves, and those in which slow waves predominate over spikes, all suggest a subcortical origin for the epilepsy and an association with some diffuse pathological process in the past—infective, toxic, or degenerative. The more severe the pathological process the longer the epilepsy has lasted, and the more severe it has been the greater the likelihood that, in addition to these subcortical discharges, there will be random cortical foci of discharge as well. These were cases called by Jasper (1949) the "diffuse dysrhythmias." They always suggest diffuse brain damage.

As in primary cortical epilepsy, so in the subcortical epilepsies the single routine E.E.G. may show no specific features and be of little diagnostic value. There may be excess slow activity related to recent seizures or to the post-ictal confused state of the patient, or, again, this pattern may be the result of medication. Focal irregular slow activity recorded in a single E.E.G. following a seizure may reflect the post-ictal state of the cortex near to the focus and *not* indicate, as it otherwise might, a cerebral tumour. It is therefore necessary to interpret the E.E.G. findings in the light of the patient's clinical state at the time the record is made. To elicit discharges, to observe their location and morphology, and so to observe which physiological systems are involved in the discharge, and further to study the background activity, it may be necessary to plan an E.E.G. study under conditions in which the different variables are known, if not controlled. Medication may have to be withdrawn, seizures may have to be elicited and witnessed, activating procedures known to stimulate cortical foci or subcortical systems may have to be used. For this reason I suggest that the value of the E.E.G. in the diagnosis of epilepsy depends upon how it is used and with what end in view. The practice of taking single E.E.G. records, unrelated to the clinical problem which the patient presents, and often without knowledge of that problem, is a procedure of little value in most cases and may be frankly misleading. E.E.G. investigations should perhaps be reserved for those patients in whom such investigations can answer certain specific questions. Such investigations have to be planned, and will perhaps involve several hours' work under varying conditions. They can, however, provide understanding of the nature of epilepsy which no other method can do.

Illustrative Cases

Case 1: Figs. 1 and 2.—Male, aged 52, with three months' history of convulsions with remembered aura of twitching of lower lip and three weeks' history of focal motor attacks arising in the right face and spreading to right arm and leg. Two weeks' progressive right hemiparesis with mental deterioration. Examination showed right hemiparesis affecting face and arm more than leg. *X*-ray film of skull and lumbar encephalogram, normal. Left carotid arteriogram showed middle cerebral artery depressed and pathological circulation in the posterior frontal areas. Biopsy: glioblastoma multiforme.

Case 2: Fig. 3.—Male aged 18. Since the age of 13 has had a number of minor attacks without warning in which he appears dazed. A history of cyanosis after birth following a bad forceps delivery. Examination showed no abnormal physical signs. *X*-ray film of skull normal. Lumbar encephalogram showed mild left hemiatrophy mainly affecting the left middle cerebral artery territory.

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MEDICAL TREATMENT IN EPILEPSY*

BY

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Various drugs were used by ancient and mediaeval physicians in the treatment of epilepsy, but the treatment methods of those times were mainly the invocation of supernatural powers and the administration of substances which had magical properties. The pharmacological approach to the treatment of epilepsy did not begin until the middle of the nineteenth century. On the occasion of the presentation of a paper on the treatment of epilepsy by E. H. Sieveking before the London Medico-Chirurgical Society on May 11, 1857, Sir Charles Locock, the presiding officer, remarked that, since the seizures in epilepsy were often related to hysteria or the menses, he had been led to try bromide of potassium. He had used bromides successfully in a case of epilepsy associated with sexual excitement after all other medications had failed. In 14 or 15 additional cases bromides had failed in only one.

Bromides were the standard therapy for epilepsy until 1912, when Hauptmann administered phenobarbitone to his patients as a sedative. He was greatly pleased to find that it had an anticonvulsant activity equal to or greater than that of the bromide. The next significant advance in the pharmacological therapy of epilepsy came with the introduction of diphenylhydantoin (phenytoin) (Merritt and Putnam, 1938). Since that time a large number of compounds have been tested in patients. Many of these have been discarded as valueless or too toxic, but a few have added greatly to our ability to manage patients with seizures.

General Principles of Therapy

The treatment of patients with convulsive seizures is divided into three parts: first, the removal of any factors, organic or psychological, that may be playing a part in the occurrence of seizures; second, regulation of the physical and mental hygiene; and, third, the administration of anticonvulsant drugs.

The surgical and psychological aspects of epilepsy are discussed by Dr. Penfield and Lord Cohen. My remarks are confined to the medical therapy.

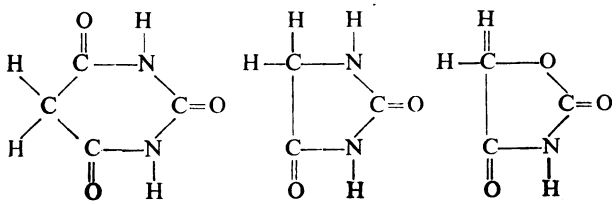
The objective of all anticonvulsant therapy is to establish and maintain a reservoir of drug sufficient to control the

*Read to the Section of Neurology at the Annual Meeting of the British Medical Association, Newcastle upon Tyne, 1957.

seizures without producing significant side-reactions. The ideal anticonvulsant—one which would affect all seizure types, have an established dosage, and produce no untoward effects—is not yet available. Consequently, choice must be made from a group of drugs, one or more of which is most effective for a particular seizure type or for a particular patient. When more than one type of seizure is present a combination of drugs is usually more effective than a single one. In fact, a combination of drugs will often be necessary even for patients with a single seizure type.

Chemical Structure of Anticonvulsants

The majority of anticonvulsants in common usage to-day are derivatives of barbituric acid, hydantoin, or oxazolidinedione. The structure of these compounds is shown in the accompanying formulas. Barbiturates and hydantoins are



Malonylurea (Barbituric acid) | Glycolyl urea (Hydantoin) | Oxazolidinedione

cyclic derivatives of urea. The oxazolidinedione ring has a superficial similarity to that of hydantoin but it is not a urea derivative. Other anticonvulsants commonly used at the present time include: primidone ("mysoline"), which has a structure similar to that of phenobarbitone but the oxygen attached to the carbon in the 2-position is replaced by hydrogen; succinimide derivatives; and carbonic anhydrase inhibitors.

Technique of Drug Administration

Medical Therapy for all Types of Seizures, Except Petit Mal.—The initial drugs of choice for major seizures, partial seizures, and psychomotor seizures are phenytoin sodium and/or phenobarbitone. These drugs have been shown to have a high therapeutic index with a minimum of untoward side-effects, and are commonly regarded as standard anticonvulsant drugs. When toxic reactions to these drugs do occur they are rarely serious, and are reversible when administration of the drugs is discontinued or dosage adjusted. In patients with infrequent seizures, phenobarbitone may prove effective by itself and, in such instances, usually is the drug of choice. In patients with more frequent attacks, phenytoin sodium usually is preferred as the initial drug, with phenobarbitone added at such time as phenytoin sodium proves ineffective as the sole agent. When both are incapable of producing the desired result the addition of other drugs, such as methoin ("mesontoin"), primidone, or methylphenobarbitone ("prominal"), is indicated.

Phenobarbitone

The initial dose of phenobarbitone for adults is usually 0.1 g. a day, given as a single dose at bedtime. If necessary the dose may be gradually increased to 0.3 to 0.4 g., administered in divided doses. Rarely will beneficial effect be obtained with larger dosage without many undesirable side-effects. Children over 2 years of age usually require the same doses as adults, and they tolerate the drug equally well. For children under 2 the dose should be computed on the basis of body weight.

The toxic effects seen with phenobarbitone are usually not serious, and are reversible when the drug is withdrawn or reduced in dosage. Drowsiness and lethargy are common at the onset of treatment and at higher dosage levels. In most instances these symptoms spontaneously disappear with the continued use of the drug. If they do not, amphetamine sulphate, 5 to 20 mg. daily, or other suitable amphetamine derivatives, can be added. An allergic rash may occur at any time, even as late as ten years after institution of treatment with phenobarbitone. In the higher dosage range, ataxia of gait, vertigo, blurring of vision, and drowsiness occur with great frequency.

Phenytoin Sodium

The initial dosage of phenytoin sodium is 0.1 g. two or three times a day, best given after meals. It is then increased by 0.1-g. increments at weekly intervals until optimum effect is obtained. In order to avoid a complicated schedule of dosage, the total daily amount of drug may be given as one dose or divided in two; giving half after breakfast and half after the evening meal. Most adults will tolerate between 0.4 and 0.6 g.; occasionally, patients may tolerate as much as 1 g. So critical is the optimum level of tolerance that 50 mg. may be the difference between seizure control and toxicity. Careful adjustment of dosage by trial and error must be carried out in each individual patient. In children under 6 years of age the starting dose is 32 mg. three times daily; in those over 6, 0.1 g. twice daily.

The toxic effects of phenytoin sodium may be divided into those which are minor and do not interfere with treatment and those which are so disturbing to the patient that administration of the drug must be discontinued. The latter are infrequent. Gastric distress and nausea may occur with the initial doses. This is minimized by taking the drug at meal-times or with sodium bicarbonate. Transient nervousness, sleeplessness, and a feeling of unsteadiness are occasionally encountered during the first few days of treatment but subside with continued use. Nystagmus develops in most patients taking phenytoin sodium; this in itself is not serious and does not constitute a true toxic reaction. When this is associated with diplopia and ataxia of gait and limbs, reduction of the dose is necessary. Usually, reducing the dose by 0.1 g. will alleviate these symptoms if they are mild. If they are more intense, cutting the dose in one-half for three to five days will be necessary. When the symptoms have subsided, the dose can be slowly increased again to a level just below that at which toxic reactions previously occurred.

Hypertrophy of the gums is a toxic effect uniquely seen with phenytoin sodium. It is distressing because of its cosmetic effects and its effect on dentition. It is primarily seen in children and young adults and does not occur in edentulous areas of the gums. It varies from slight puffiness and sponginess of the gums to hyperplasia that may completely bury the teeth. It bears no relationship to dosage and is rarely seen in the first few months of treatment. Good dental hygiene, with vigorous massage of the gums, should be practised by all patients taking phenytoin sodium, as this seems to retard the process. When excessive overgrowth occur, surgical excision is indicated. Rarely will administration of the drug have to be discontinued because of this finding.

Hirsutism is occasionally encountered in children. In adolescent and pre-adolescent girls this is a disturbing symptom and may necessitate withdrawal of the drug; however, it is mild in most instances. Since it does not disappear with elimination of therapy, administration of the drug should not be discontinued unless this symptom is noted to be progressive.

Major allergic phenomena, such as fever, polyarthropathy, and skin eruptions, are rare, but they are causes for a change in anticonvulsant medication when they occur. The skin eruptions seen with phenytoin sodium are of two varieties. The first is an acute generalized morbilliform eruption with or without rise of temperature, usually occurring about ten days to two weeks after treatment is begun. Withdrawal of the drug results in complete alleviation of this toxic manifestation. The second type of eruption is an exfoliative dermatitis, which may occur at any time in the course of the treatment. Though retrial beginning with smaller doses and increasing by smaller increments may be attempted, the chances of success are remote. It is best to employ one of the other anticonvulsants.

Additional Drugs

Many new compounds have been given a clinical trial in recent years. Some have been discarded because of lack of anticonvulsant activity or because of serious untoward side-effects. A few of the new compounds, however, have proved of value when used in combination with phenobarbitone or phenytoin sodium. The use of these compounds is indicated when an adequate trial of phenytoin sodium and/or phenobarbitone has failed. Adequate trial of these two drugs implies the administration of these in combination with increasing doses until the appearance of untoward side-symptoms make further additions in dosage inadvisable. When control of seizures cannot be obtained with maximum tolerated doses of phenobarbitone and phenytoin, one of the new compounds may be added, starting with a small dose and gradually increasing as indicated. Administration of a previously tolerated, although apparently ineffective, anticonvulsant should not be abruptly discontinued, except in the rare instances of an acute allergic reaction, until a full dosage level of the newer drug has been attained. In most instances, administration of the initial drugs will need to be continued. In refractory cases a combination of three or four drugs may be required.

Methoin.—When methoin is used as the sole anticonvulsant for adults, a dosage of 0.4 to 1 g. is usually required. Therapy is started with 0.1 g. of the drug three times a day, and the dose is gradually increased by 0.1-g. increments at weekly intervals. When the drug is being added to an existing anticonvulsant regimen, 0.1 g. a day is given initially, with 0.1 g. being added at weekly intervals. In children under 6 years of age half doses are used : 50 mg. three times a day. Drowsiness is a frequent side-effect with methoin, and often limits its use in full therapeutic doses. Allergic skin eruptions occur more often than with the use of phenytoin and necessitate withdrawal of the drug. The most serious toxic effect of methoin is a blood dyscrasia —agranulocytosis, pancytopenia, and aplastic anaemia— which may be fatal. Though the highest incidence of this blood dyscrasia is during the first few months of treatment, it may occur at any time in the course of therapy. For this reason all patients taking this drug should be examined frequently and have a complete blood-cell count once a month throughout the period of treatment.

Methylphenobarbitone.—This is mainly used as a substitute for phenobarbitone. In equivalent dosage its sedative effect is less than that of phenobarbitone, and it must be used in higher dosages to match the anticonvulsant action of phenobarbitone. It is therefore employed in double the phenobarbitone dosage ; its side-effects are similar.

Primidone.—The starting dose of primidone is 0.25 g. daily, increasing by 0.25-g. increments at weekly intervals. In order to achieve therapeutic effectiveness, 0.75 to 1.5 g. daily is usually required. In children one-half the adult dose is used. Drowsiness, nausea, vomiting, dizziness, and ataxia are toxic manifestations. In most patients these symptoms subside with regulation of the dosage, but on occasion withdrawal is necessary. In most instances primidone cannot be given in large enough amount to achieve seizure control without undesirable side-effects. Consequently, it rarely can be used by itself but must be combined with other drugs, usually phenytoin sodium.

Acetazolamide (" *Diamox* ").—The use of carbonic anhydrase inhibitors as anticonvulsant agents is relatively recent. In addition to inhibiting brain carbonic anhydrase, acetazolamide has acidifying and dehydrating properties. To which of these properties its anticonvulsant action can be attributed is unknown. Reports concerning the use of acetazolamide are few and vary as to the seizure types affected. In adults the starting dose is 0.25 g. three times a day, with gradual increase by 0.25-g. increments up to 1 g. Large doses may produce drowsiness and paraesthesia in the face and limbs. These symptoms disappear with reduction of dosage. Isolated instances of agranulocytosis, thrombocytopenia, and renal lesions, some fatal, have been reported during the short time this drug has been in use.

Phenacemide (" Phenurone ").—Phenacemide is of extremely limited use because of its serious toxic effect. It may be tried as a last resort in patients with severe and frequent psychomotor seizures in whom seizure control cannot be obtained with other drugs. In adults the starting dose is 0.5 g. three times a day. Its therapeutic dosage range is 2 to 3 g. a day. In children half doses are used— 0.25 g. three times a day. Phenacemide may produce serious toxic reactions, including personality disturbances with psychotic manifestations, toxic hepatitis, and blood dyscrasias. Some of these reactions may be irreversible and fatal ; hence utmost care must be exercised during use of the drug. Patients taking phenacemide should be examined frequently and have periodic blood counts and liver-function tests. Use of the drug is contraindicated in patients with a history of previous psychoses or liver disease. Other toxic phenomena seen with phenacemide include nausea, vomiting, skin eruption, and drowsiness. In some instances these may be alleviated by adjustment of dosage, but may also be severe enough to require withdrawal of the drug.

Combined Drugs.—Combinations of one of the hydantoins and barbiturates (with or without a stimulant to inhibit sedation) have been made available for ease of administration of these drugs. Their use is exceedingly limited under the programme of drug administration as outlined previously, because the dosage of one cannot be adjusted without affecting the other. They can be used in the rare instances where a patient's condition has been stabilized on a combination of drugs, and the individual dosages fortuitously correspond to the fixed ratio of dosage in the combination. The dosages of hydantoin and barbiturate (also combined with added methamphetamine) as provided by three such combinations are detailed as follows: (1) phenytoin sodium, 60 mg., and methylphenobarbitone 90 mg. ; (2) phenytoin sodium, 100 mg., phenobarbitone, 30 mg., and methamphetamine hydrochloride, 0.25 mg. ; and (3) methoin, 100 mg., and phenobarbitone, 20 mg.

Petit-mal Epilepsy

For success in the treatment of petit mal it is important to distinguish this seizure from other minor seizure types. Rigid adherence to the characteristics described by Dr. Williams (p. 661) and electroencephalographic confirmation are necessary. The drugs commonly used for the treatment of petit-mal seizures are derivatives of oxazoledine and succinimide. These drugs are not effective against other types of seizures and are thought by some to precipitate major seizure phenomena. When petit mal coexists with other seizure types, adequate therapeutic doses of phenobarbitone and phenytoin sodium are indicated as well.

Troxidone (" Tridione ").—The starting dosage is 0.3 g. three times a day for adolescents and adults. Gradual increases in dosage are carried out until therapeutic effect is obtained, usually between 1.5 and 2.7 g. daily. In children under 2 years 0.15 g. two or three times a day is the initial dosage, with increments of 0.15 g. The limiting minor side-reactions seen with troxidone are photophobia, drowsiness, and nausea. The photophobia may disappear with continued therapy or be controlled by the use of dark glasses. Drowsiness and nausea are self-limited, and spontaneously remit with continued therapy. Toxic dermatitis occurs with some frequency and is of the morbilliform or urticarial variety. The drug should be withdrawn immediately when rash appears, but it may be tried again, beginning with smaller doses and increasing by smaller increments at a slower rate. The serious toxic reactions seen with troxidone are aplastic anaemia, agranulocytosis, and nephrosis. A number of fatalities due to these complications have occurred ; therefore it is necessary that all patients taking this drug be examined frequently and that monthly blood-cell counts be performed. Transitory decreases in the percentage of polymorphonuclear leucocytes without an absolute decrease in total leucocytes may occur during treatment

with troxidone. This does not necessitate withdrawal of the drug but requires added caution and more frequent blood-cell counts. The appearance of signs of kidney dysfunction requires immediate withdrawal of the drug.

Paramethadione ("Paradione").—Paramethadione is a close analogue of troxidone. Its dosage schedule and toxicity are similar. Toxic manifestations are less frequent, and intolerance to troxidone does not necessarily mean intolerance to paramethadione. Its use is indicated in those patients with petit-mal seizures who are refractory to treatment or develop toxic reactions to troxidone. Occasionally the combination of both drugs gives better results than either one alone. The same precautions that were detailed for troxidone apply to the use of paramethadione.

Phensuximide ("Milontin").—This is indicated for the treatment of petit mal when troxidone and paramethadione, administered either alone or in combination, have proved ineffective. The starting dose is 0.5 g. three times a day, with gradual increases of 0.5 g. Therapeutic effect is usually obtained in the range of 2 to 3 g. a day. The limiting side-effects are nausea, vomiting, dizziness, drowsiness, and dreamlike states. These disappear with adjustment of dosage or withdrawal of the drug. Transient microscopic haematuria has been reported during its administration, but all investigations are not in agreement regarding occurrence or significance. It would seem wise to do urinalyses and blood-cell counts at stated intervals for patients receiving the drug for long periods until more is known about its toxic manifestations.

Causes of Failures of Therapy

The success in the use of anticonvulsant drugs is related to the degree of skill used by the physician in administering the available drugs. Failure to obtain the optimum results in therapy are related to a number of factors : failure to recognize a progressive neurological disease, particularly brain tumours ; failure to use proper drugs ; failure to administer proper dosage ; premature withdrawal of drugs ; frequent shifting of drugs ; poor indoctrination of patient in regard to the therapy ; and lack of recognition of social and economic needs of patient.

The largest number of failures are related to failure to administer the proper amount of the drug and failure to use two or more drugs in combination. There is no established dosage of any of the anticonvulsant drugs. The guiding rule should be to start with a small or moderate dose of the drug which is considered to be suitable for the patient, with gradual increase of dosage at suitable intervals until the seizures are controlled or the appearance of minor toxic symptoms make further additions inadvisable. If serious toxic symptoms develop, the drug should be withdrawn and another substituted. If the drug used initially is well tolerated but is not capable of controlling the seizures, another compound should be added. Usually large doses of each drug are needed when two or more drugs are used.

Success of Anticonvulsant Therapy

The results of treatment in 319 cases of epilepsy were : controlled, 154 (48%) ; improved, 118 (37%) ; and uncontrolled, 47 (15%) (Yahr *et al.*, 1952). These results are good when compared with those which could be obtained 25 years ago, but they are still inadequate. New compounds are being tested regularly, and it is quite probable that a more effective therapy will be available in the near future.

The question arises of when it is advisable to withdraw medication in patients who have been under therapy and have had no seizures for many months or years. Some children and young adults may have a few seizures in the course of a year or two and then have a complete remission. Spontaneous remissions may also occur in patients who have had seizures for many years. It is also possible that a remission may be induced by the treatment. It is our rule to administer anticonvulsants to patients with any type of seizure except petit mal for a period of at least three years after all seizures have disappeared. At this time the dose of the drug can be reduced every four to six months by one-third to one-fifth of the amount required to control the seizures. If seizures recur the drug should be readministered in full dosage. The results (see Table) obtained in the attempt to discontinue anticonvulsant therapy in patients who had been seizure-free for a prolonged period have been disappointing, except for those with petit mal attacks (Yahr and Merritt, 1956).

Results of Reduction and Elimination of Medication in Various Types of Seizures

	Total No.	Seizure-Free		Recurrences	
		Off Medication	On Reduced Dosage	Off Medication	On Reduced Dosage
Petit mal	14	12	2	—	—
Grand mal and other	71	17	19	9	30

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PITFALLS AND SUCCESS IN SURGICAL TREATMENT OF FOCAL EPILEPSY*

BY

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In the earliest days of the specialty of neurosurgery, excision of cortex was tried, but soon fell into disrepute, as a method of treating epileptic seizures. Recently, however, the method has slowly returned to respectability, thanks to growing understanding and better methods.

In 1922 I began to make brain wounds experimentally and to study the healing process. In 1927 I operated for the first time (one case) to remove an area of scarred brain, in the hope of curing the patient of his "traumatic epilepsy." That was in the Presbyterian Hospital, New York City. Rumour reached me then that Otfried Foerster was operating on such patients in Breslau. So I spent six months in his clinic in 1928. Here was something better than the useless methods in vogue at the time, covering the scars with various substances. Fortunately for me, his surgical specimens had not yet been studied, and so I set to work to cut microscopical sections of the material he had removed radically from the brain of some 12 sufferers. He allowed me to join him in the publication of those first cases (Foerster and Penfield, 1930a, 1930b). On leaving Germany I made my home in Montreal, and have since spent an increasing amount of time in operating-room and laboratory, working on this problem.

Clinical electroencephalography made its appearance about 1936, after the pioneer observations of Berger, Adrian, and others. This served to enlarge the field, and, slowly by means of medical team-work, a rational system of radical therapy has come into existence, replacing the previous hit-or-miss surgical procedures.

To-day, my associate Theodore Rasmussen and I have splendid help and guidance in electroencephalography

*Read to the Section of Neurology at the Annual Meeting of the British Medical Association, Newcastle upon Tyne, 1957.