Clinics in Developmental Medicine No. 16

Drugs in Cerebral Palsy

Based on a Symposium held at Dallas, 24-26 November, 1963

Authors
Eric Denhoff
Patrick Hume Kendall
Amedeo Marrazzi
John Nodine
Meyer Perlstein
Winthrop Phelps

Edited by
Eric Denhoff

1964

$4 or 25s.

Published by The Medical Education and Information Unit of The Spastics Society in Association with William Heinemann Medical Books Ltd.

Dedicated to

John Fitzgerald Kennedy

Contributors

Eric Denhoff	Medical Director, Meeting Street School Children's Rehabilitation Center, Chief of Pediatrics, Miriam Hospital, Providence, Rhode Island, U.S.A.
Patrick Hume Kendall . .	Head of Department of Physical Medicine and Head of Cerebral Palsy Assessment Centre, Guy's Hospital, London, S.E.1. England.
Amedeo S. Marrazzi	Director, Veterans Administration Research Laboratories in Neuropsychiatry, Professor of Physiology and Pharmacology, University of Pittsburgh School of Medicine, Pittsburgh, Pa., U.S.A.
John H. Nodine	Assistant Professor of Medicine, Director of Special Medical Clinic, Head of the Section of Clinical Pharmacology, Department of Medicine, Hahneman Medical College and Hospital, Philadelphia, Pa., U.S.A.
Meyer A. Perlstein	Associate Professor of Pediatrics, Northwestern University Medical School, Professor of Pediatrics, Cook County Post-Graduate Medical School, Chicago, Ill., U.S.A.
Winthrop M. Phelps	Medical Director, Children's Rehabilitation Institute Reisterstown, Maryland, U.S.A.

Preface

This book is one of the first fruits of a recent Anglo-American alliance — the arrangement by which the journal 'Developmental Medicine and Child Neurology' and the American Academy for Cerebral Palsy are linked. The journal's sister publications, these Clinics in Developmental Medicine, have found favour with many people on this side of the Atlantic and we hope this volume, the first to include work by many well-known American writers in the field, will make the series more widely known on the other side of the Atlantic. We are grateful to the American Academy for Cerebral Palsy for suggesting that a book should arise out of the Symposium on Drugs in Cerebral Palsy which the Academy arranged at its Annual meeting in November, 1963.

As Meyer Perlstein suggests in his chapter, men have been trying to solve their problems with drugs for a very long time. Perhaps our task is to start by issuing a word of warning on drug treatment before recommending this book to readers. All drugs work by selective poisoning of enzyme systems and therefore all drugs that work at all are toxic to a greater or lesser extent depending on the dosage and the state of the person to whom the drug is being administered. As Eric Denhoff points out, a great deal of harm can ensue from the administration of the wrong drug just as good can flow from the administration of the right one. In their introductory chapters John Nodine and Amadeo Marrazzi point to the many problems of drug evaluation, both in general and in cerebral palsy. It is particularly important to draw attention to the fact that human responses to a drug cannot be predicted from those of animals. Moreover, the response of one human to a drug may differ quite sharply from that of another.

The administration of a drug has long term effects which may not be immediately apparent. For example, a patient who has had drug A prior to the administration of drug B, may respond quite differently to drug B from the patient who has not had any previous medication. These, and many others, are general reasons for restraining the arm from reaching out too freely for the prescription pad. And in cerebral palsy one must recall that a portion of the nervous tissue is dead and that no drug can or will cure the condition. One's first duty as a physician and as a friend to the cerebral palsied patient and his parents is to help them to appreciate this situation. One needs to have all these provisos in one's mind before one embarks on any book on drug treatment. For, despite the caution of the authors, the reader tends to act on the positive suggestions and to neglect the negative warnings.

After this word of caution the other point to emphasise is the importance of assessment. Dr. Nodine's chapter sketches in the general principles underlying drug evaluation and Dr. Phelps, in his short but practical paper, suggests one way in which practical assessments of patients can be made from day to day. This may seem time consuming but can only benefit the patient in the long run.

The three main spheres where one might expect drugs to be helpful to the cerebral palsied are epilepsy, behaviour disorders and disordered muscle tone. The first con-

dition is the one on which specific statements can be made. A cerebral palsied child with epilepsy should be treated with drugs and the epilepsy controlled. With other conditions it is difficult to make such imperative statements. As Dr. Denhoff suggests, skilled use of the armentarium at the physician's disposal can affect the behavioural problems which children with cerebral palsy, and their families, are heirs to. Patrick Hume Kendall is rightly cautious when he discusses the effects of drugs which have been claimed to reduce muscle spasms; no ideal substance exists at the present time, although there are drugs which definitely do have valuable effects.

It is appropriate that the lion's share in the editing of this book should have been borne by Eric Denhoff, as he is this year's President of the American Academy for Cerebral Palsy. Interest in cerebral palsy has increased markedly over the last decade and this has been due to the activities of the Academy and this increased interest is due in part to the calibre of the officers of that organisation. We would like to thank Dr. Denhoff for his hard work on the manuscript. It reflects the energy and devotion which he has put into his year as President of the Academy.

Martin C. O. Bax, R. C. Mac Keith 1964.

CHAPTER 1

Introduction

ERIC DENHOFF

Drug therapy is one important aspect of the treatment of cerebral palsy and related disorders. Medication alone is, of course, insufficient to control the variety of problems which make up the syndromes of cerebral palsy. But pharmacological aids have an important place in any treatment programme. They are, for example, effective if used before the secondary symptoms have so distorted the basic conditions as to make it difficult to change the course of the disease. In infancy or early childhood, muscle relaxant drugs used conjointly with physical therapy make it much easier to treat postural deformities than it is later when fixed contractures are present. Similarly it is relatively easier to control hyperkinetic behaviour with medication if it is recognised earlier rather than later in childhood, when secondary family problems exist which may stem from an unrecognised and untreated hyperkinetic behaviour component.

Our concept of cerebral palsy has expanded from a limited one of 'neuromotor disability resulting from brain damage' to include a spectrum of neurological dysfunctions which include neuromotor, intellectual, convulsive, behavioural, sensory and perceptual components. The type of the neuromotor disability, the severity, and the anatomical distribution identifies the case both as cerebral palsy and the type. When other components assume greater clinical significance, then these are identified appropriately as mental retardation, epilepsy, hyperkinetic impulse disorder, or visual-motor perceptual disability. These latter conditions are related to cerebral palsy, and the conglomerate is designated as Syndromes of Cerebral Dysfunction (Denhoff and Robinault 1960).

The importance of understanding this broadened concept prior to treating a case of cerebral palsy appears obvious. It is not the purpose of this book to discuss in detail the various forms of cerebral dysfunction, and accounts of the components of the various dysfunctions are necessarily brief; but in order to achieve some measure of success with drug therapy it is necessary to understand and treat simultaneously the various components involved in a particular case. One must, for instance, recognise the presence of a strong emotional element in both the child and his family, and these factors must be included in the treatment plan.

Drugs are useful to control convulsions when present, to help overcome behaviour manifestations which interfere with achieving optimum results from the various therapies, to influence beneficially abnormal neuromotor states which interfere with developmental progress, to correct metabolic insufficiencies, and finally, to help parents recognise their child's potentialities or limitations (Denhoff 1964)

An ideal single drug for cerebral palsy has not yet been developed and in lieu of the 'ideal' medication, various drug combinations are given to try to fit the particular needs of the patient. Often such combinations include an anticonvulsant, a behaviour

modifier and a skeletal muscle relaxant. This means that cerebral palsied children frequently may be on several medications at one time. Since these children are often difficult to give medication to, the inference is that they may not always receive all of the prescriptions. This is one important reason why the search for better and more effective drugs must continue.

REFERENCES

Denhoff, E., Robinault, I. P. (1960) Cerebral Palsy and Related Disorders. New York: McGraw Hill.
—— ——, (1964) A Pharmacological Approach to Cerebral Palsy, presented at the Symposium or Skeletal Muscle Hypertonia. Boston, Mass. January 22-23, 1964 (to be published).

CHAPTER 2

General Principles of Drug Evaluation

JOHN H. NODINE

In cerebral palsy a wide variety of symptoms and disturbances may be present; not only are there neuromuscular disturbances but intellectual and emotional function may be disturbed as well. Consequently, drugs which affect brain enzyme function may be important for evaluation and use in cerebral palsy, as well as the broad group of neuropsychopharmacological agents. More specifically, drugs which affect intermediary metabolism, anticonvulsants, sedatives, antitremor agents, central skeletal muscle relaxants, tranquilizers, psychic energisers or anti-depressants, stimulants, analgesics, and possibly even psychotomimetic agents may be considered for clinical evaluation and use in various children with cerebral palsy, depending the specific symptoms and disorders present. Drugs will always remain only a minor part of the total treatment programme in patients with cerebral palsy but the development of many new agents falling into the above categories has stimulated interest in the use of drugs and in the clinical investigation of some of the more specifically acting compounds which have become available in recent years. More will become available in the not too distant future.

Pre-Clinical Studies

During the past decade, remarkable progress has been made in the development and expansion of the general field of neuropsychopharmacology. Countless compounds have been and are being synthesized and screened to determine their activity in animals, and many new investigative techniques have been developed using both animals and man (Nodine and Moyer 1962). Ordinarily the chemist follows a plan of molecule manipulation to develop a series of compounds related to compounds of known activity, or he may work with an entirely new group of compounds which are then subjected to general animal screening. When significant neuropsychopharmacologic properties are found, more detailed studies are carried out in animals in order to pinpoint the site of action, to understand better the mechanism of action, and to determine the relative potency of the new compound compared with existing compounds with similar types of action. Unfortunately, the techniques available for the study of neuropsychopharmacological agents in animals do not allow us to predict the effect of the drugs in humans. Actually most of the major agents developed in the past ten years have resulted from clinical observations which were not anticipated from the pre-clinical studies in animals. Examples include the tranquilising and anti-psychotic effect of chlorpromazine (Thorazine R), the anti-depressant effect of the monamineoxidase inhibitors and the anti-depressant effect of imipramine (Tofranil R).

When a compound appears interesting pharmacologically it is studied for its toxic effects in animals. The acute lethal dose range (LD50), and its subacute and

chronic effect on animals of several species are evaluated. For the chronic toxicity evaluation different dosages are used in different animals over a significant period of time, and some dose is used which actually causes symptoms or damage to the animals receiving it. By this means the type of toxic effect which may be encountered in man and the general tolerance level of the compound are estimated.

Clinical Evaluation

Although the ideal aim of all studies evaluating drug effects in man is to cure disease, in most drug research we must be content to alter pathological physiology or to eliminate symptoms. As more knowledge is gained about pathophysiological mechanisms, our pharmacological attacks may become more basic. In addition to the main symptoms or disturbance being evaluated, the investigator must be alert to unexpected side effects and to the amelioration of associated conditions. *An astute clinical investigator with a thorough knowledge of disease, pathophysiology and pharmacology is most essential in any experimental design in clinical pharmacological research.* Although new drug evaluation in man is divided into three phases, individual ingenuity must be used since most commonly two of the three stages can be carried out in combination or simultaneously. The three phases are as follows:

Phase 1 — Acute Human Pharmacology.

This phase is limited to relatively few patients and aims to explore (i) the dose range which is required to produce pharmacological effects; (ii) the dose range which cannot be tolerated after acute administration, as well as the particular side effects which have resulted in this intolerance. The first dose to be given to man is selected on extremely conservative criteria. It is so small that no significant risk is encountered. The exact dose is selected by a careful evaluation of all of the available animal data. In our unit a research committee reviews each drug protocol to assure that optimum safety and the best experimental design are used in evaluating the drug. The detailed criteria for the selection of dosage are presented elsewhere (Nodine 1964.)

Even when the drug has been previously administered to normal volunteers, patients with disease or children may react differently, so that *it is necessary to carry out a Phase* 1 *Acute Study in the type of patients in whom the drug will eventually be used.* Generally one or two subjects are given each dose level and the dose is doubled when no significant toxic effects are encountered.

Phase 1 is designed primarily to obtain information regarding acute tolerance to the drug, relatively little emphasis being placed on its therapeutic potential. In addition it may serve as a means for comparing the relative potency of several similar agents, belonging to a particular class of drugs, in order to select for more detailed evaluation the one which seems to be most potent in man. In this phase considerable variability in design is anticipated since doses are changed from day to day depending upon the results of the previous day's studies. A drug is not eliminated from further study by Phase 1 results, since the therapeutic potential is not fully explored. Tolerated doses are selected for Phase 2 unless one of several analogues is chosen for further investigation.

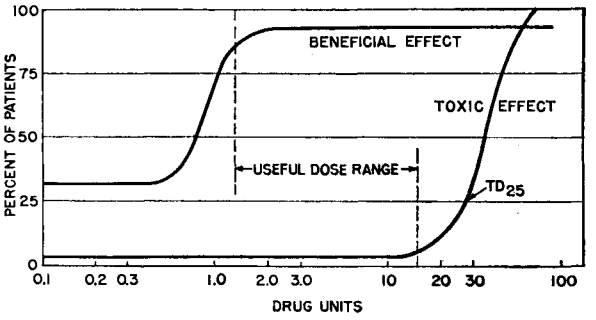


Fig. 1. Human bioassay of a "good" drug.

Phase 2 — Exploratory Bioassay.

Phase 2 is essentially a human bioassay designed to explore the usefulness of the drug on acute or subacute administration to a group of patients suffering from a particular symptom or group of symptoms. The effective clinical dose has not been determined, nor has the subacute tolerance of the drug in patients suffering from the condition being treated. In this early exploratory stage it is wise to use a spectrum of conditions which may conceivably respond, treating a number of patients with each condition, using multiple doses and individual dose adjustment in order to achieve the maximum beneficial effect in each patient with a minimum of side-effects. Some relationships should be established in this phase. Unfortunately, we may be dealing with a type of dose-response curve which commonly does not follow the classic patterns, which have been subjected to detailed statistical analysis and from which the ED50 (effective dose for 50 per cent of the patients) in man can be determined along with its confidence limits.

Figure 1 illustrates the type of dose-response curve commonly encountered with an 'effective' drug. A certain fraction of patients will commonly respond, by whatever criterion of response is appropriate for the particular drug, because of placebo effect or spontaneous recovery during the time period when the drug is administered. With most conditions, a certain fraction of the patients remains unresponsive regardless of the drug dose administered. The potency of the drug and the symptoms which respond to it must be determined from the dose-response curve of those subjects who do respond. The particular doses at which they respond are recorded. The degree of placebo response varies with the type of clinical condition being treated and the special protocol for the individual drug study; however, the unresponsive fraction is a parameter of drug response which is of value clinically (Nodine 1962, Mapp and Nodine 1962, Nodine 1963). An ideal drug would, of course, be effective in all patients, so that the unresponsive fraction would approach zero. Under practical circumstances, however, the unresponsive fraction commonly ranges from 10 to 30 per cent of the patients, so that, other things being equal, the lower the unresponsive fraction the better.

In a general screening of this type we usually push the drug to the level where 25 per cent of the patients fail to tolerate it and compare this with the percentage who fail to respond to it at all. By 'failure to tolerate' we mean that the physician or the patient is so alarmed that the physician either stops the drug or lowers the dosage.

An example of the type of curves which may be expected from administration of a good drug is shown in Figure 2, while Figure 3 is an example of the type of curves seen in a less satisfactory drug. On practically any dosage a certain percentage of patients fail to tolerate the drug because of individual idiosyncrasy, allergy or placebo toxicity. Ordinarily, this intolerance to placebo does not exceed 5 per cent, so that when 25 per cent of the patients fail to tolerate a drug one may conclude that a significant difference in tolerance has been encountered.

The useful dose range of a drug will, of course, be higher than the ED50 in man, and comprises the range where the beneficial effect curve is maximum and the toxic effect curve has not yet begun to rise. This type of curve may be plotted no matter what clinical response criteria are used and a response appropriate to the condition being studied selected. With a diuretic, the response may be freedom from oedema. In a spastic child the response may be improvement in walking or performance, and in convulsive disorders it may be freedom from convulsions. With most of the neuropsychopharmacologic agents used in cerebral palsy, the best criterion at the moment is a 'satisfactory clinical response.'

It is important that the response selected is not trivial in the conditions being treated (Nodine 1962), so that the beneficial effect curve has a direct relationship to what constitutes a satisfactory clinical response. The use of too many parameters of response may confuse the issue, and a 'statistically significant' response is observed in the absence of a satisfactory clinical response. Under these circumstances the response is not 'medically significant'.

Further investigation of drugs is dropped if there is significant toxicity, the toxic effect curve is too close to the beneficial effect curve so that the dose adjustment is difficult, or if the agent is less effective than existing standard agents in the management of the particular clinical condition being studied.

A number of laboratory studies for hepatic, renal and haematological toxicity are carried out at regular intervals despite the fact that no such abnormalities may have been encountered in animals. If particular abnormalities or organ damage were noted in the animal studies, additional laboratory observations are ordinarily carried out to guard against similar reactions in man.

During this phase, the doses used are in part dependent on the response observed during Phase 1 and in part dependent on the previous animal data which are available.

The experimental design must still remain flexible, since the effective dose range and subacute tolerance are not known at the time this type of study is initiated. The use of placebo controlled cases is not warranted, nor are many of the ancillary observational techniques described in Phase 3.

Phase 3 — Controlled Study.

The basic design of Phase 3 varies more than any other stage because it depends on the drug being studied and the specific condition or symptoms being treated. Once the experimental design has been established, however, it is important to observe it rigidly unless unusual toxicity or potentially serious findings occur. In this phase

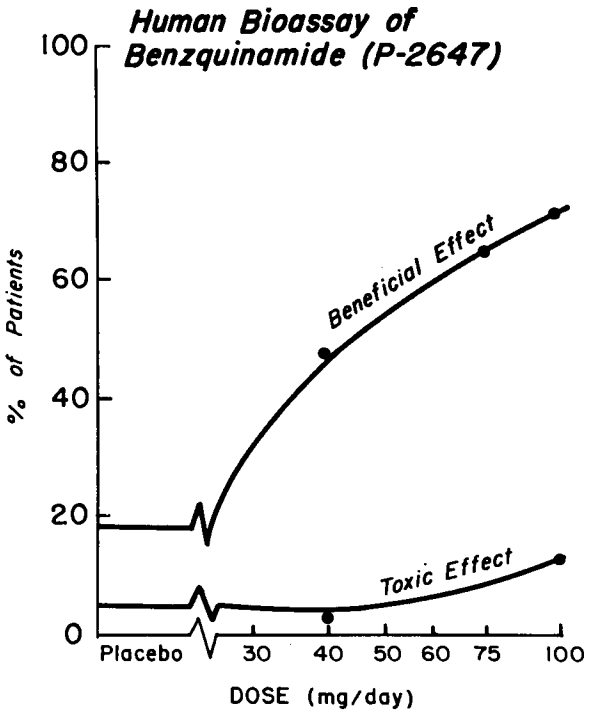


Fig. 2. Phase 2 bioassay of a drug where wide separation occurs between the beneficial effect curve and the toxic effect curve.

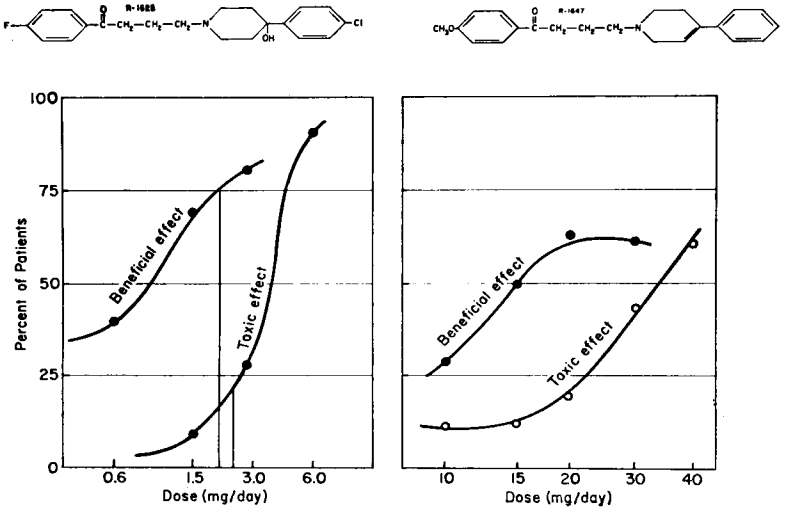


Fig. 3. Phase 2 bioassay of a drug where the toxic effect curve and the beneficial effect curve are close together.

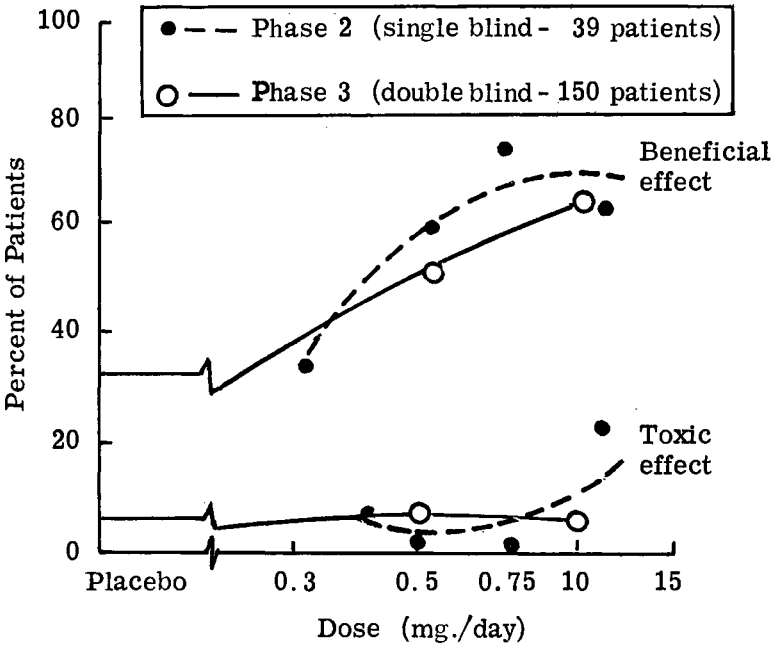


Fig. 4. Comparison of the results of Phase 2 and Phase 3 bioassay of fluphenazine in outpatient anxiety.

of drug evaluation one is seeking the place of the particular agent in the treatment of a number of specific conditions. A rigid case selection based on limited diagnostic categories or symptom complexes may be used in an effort to obtain the best possible control. When clinical response alone is being measured, a placebo group is essential. Often a standard drug is added to show that the technique is sensitive to picking up drug effect and to compare the new drug with the standard agent. Individual dose adjustment may be written into the experimental design. Where marked variability in the severity of the disease is encountered, with varied prognoses, pairing of patients in a random fashion may improve the sensitivity of the technique and decrease the variability (Nodine *et al.* 1959).

Various objective parameters — rating scales of one sort or another — may be devised in this phase of the study (Mapp and Nodine 1962, Nodine 1963), but one must not lose sight of the fact that a satisfactory clinical response is still the ideal criterion of response.

In considering the experimental design of Phase 3 the information from Phase 2 must be available in order to select the category of patients to be treated, the proper dosage or dosages of the drug, and the appropriate time intervals for observations of improvement, toxicity and side-effects. Thus the Phase 3 study may confirm or discount the findings from Phase 2 (Fig. 4). Since this type of study is time consuming and expensive, it represents scientific foolishness when two or more years are spent

in a double blind study after which one finds that too low a dosage of the new drug was selected. So many new compounds are being synthesized that clinical pharmacological facilities should not be overtaxed by needlessly complex experimental designs initiated inappropriately in the wrong stage of clinical study.

Phase 3 is an appropriate time for many investigators to attack the problems of the use of the new drug in disease conditions where its pharmacological properties seem helpful. The clinician and the research worker must co-operate closely if genuine results are to be obtained.

REFERENCES

Mapp, Y.,Nodine, J. H. (1962) 'Psychopharmacology II: tranquilizers and antipsychotic drugs.' *Psychosomatics*, **3,** 458.

Nodine, J. H. (1962) 'Psychopharmacology I: general principles.' *Psychosomatics*, **3,** 351.

—— (1963) 'Psychopharmacology III: stimulants and anti-depressants.' *Psychosomatics*, **4**, 73.

—— Moyer, J. H. (eds.) (1962) Psychosomatic Medicine. Philadelphia: Lea and Febiger.

—— (1964) 'Stages of drug evaluation in man: general principles of experimental design.' *In* Clinical Pharmacologic Techniques. ed. by J. H. Nodine and P. E. Siegler. Chicago: Year Book Medical Publishers, chap. 7.

—— Yoshizawa, H., Weiss, W., Stein, S. C., Guth, R., Tummillio, M. (1959) 'The effect of L-triiodothyronine in pulmonary tuberculosis: a pilot study.' *Amer. J. med. Sci.*, **237,** 27.

CHAPTER 3

Pharmacology of Drugs in Cerebral Palsy

AMEDEO S. MARRAZZI

The Problem

In treating cerebral palsy we must deal with the special problem of the child as a patient as well as the condition itself. Thus we are trying to manipulate therapeutically within the context of developmental physiology and pharmacology. The level of maturation, normal or abnormal, determining lowered or, more usually, elevated thresholds is a paramount factor in response to drugs. In addition, the required chronicity of medication has the associated complications of tolerance and toxicity.

More specifically the practical problems are:

1. The handling of childhood convulsions.
2. The induction of relaxation in spastic and hyperkinetic states of the motor system.
3. The improvement of behaviour.
4. Alleviation or correction of metabolic deviations.

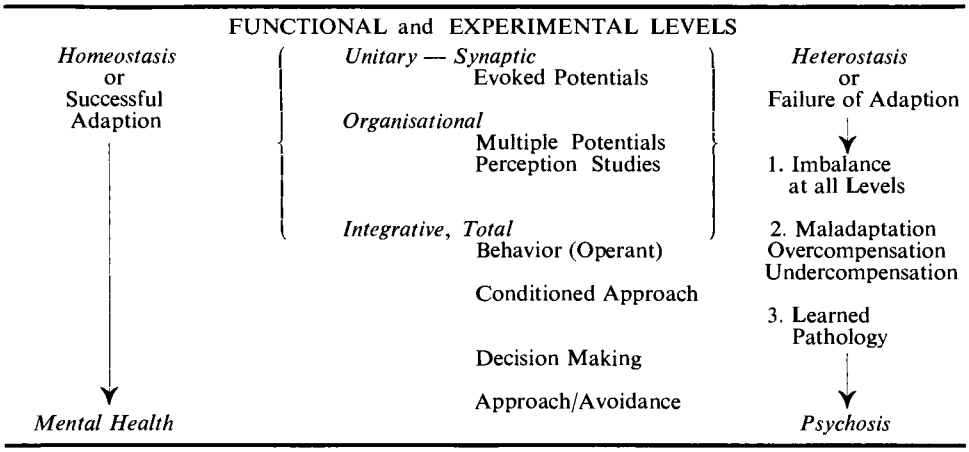
These all require, of course, an accurate assessment and detailed diagnosis. It is the potential contribution of new concepts and possible new drug developments to the above, that we wish to discuss.

Cerebral Homeostasis

Since the problems are largely those of adequate control of function, it will be profitable to look at the brain and the nervous system as a whole as the instrument for homeostasis. Such a concept of cerebral homeostasis (Marrazzi *et al.* 1963*a*) and the methods of obtaining the data upon which it is built and being elaborated is presented in Figure 1. This looks at cerebral function as a reflection of a homeostatic equilibrium normally maintained at the 'building block,' 'unitary' or synaptic level, at the organisational level, at the total integrative or behavioural level and between all the levels.

As emphasised by the title, this system is an adaptive one; so that normally, dislocations of equilibrium are transient; restoration signalling the end of the transaction with return to the original or, in the case of longer lasting adjustment, to some new level within the normal range. Homeostasis, as indicated on the left, is the basis of normal cerebral function and, in the aspect indicated here, normal mental function. Failure of homeostasis, indicated on the right, calls for maintained homeostatic endeavours to achieve the normal range which are in this case unsuccessful and therefore maladaptive. These over- and under- compensatory activities manifest themselves as an overlay of *secondary* symptoms in patterns which, when maintained over long periods, become entrenched in what we have called 'learned pathology'.

Fig. 1. Cerebral Adaptive Systems



It is therefore evident that the strategy of therapy in any sustained cerebral imbalance and its resulting dysfunction needs to be twofold — to eliminate the initiating imbalance and to eradicate the persisting learned pathology.

A communication and decision system, like the brain, is obviously best examined by putting in a known input and recording the resulting output (Marrazzi 1960*a*). Figure 2 pictures a cat's brain drawn as though transparent and indicates : (1) the position of the input electrodes, through which is delivered a small electric shock; (2) the interhemispheral (transcallosal) pathway traversed to reach the terminal synapses underlying; (3) the recording electrodes placed on the contra lateral hemisphere at a site symmetrical to that of the stimulating electrodes. In this preparation the experimental animal is lightly anaesthetised with sodium pentobarbital. After suitable amplification, the output message or evoked potential is displayed on a cathode ray screen, where it can be followed visually and recorded photographically. By such methods it is possible to monitor and study the equilibrium at synapses in any part of the brain, and, using multiple recording electrodes, the equilibrium between regions of the brain, while behaviour in the unanaethetised animal monitors overall equilibrium or total integration. The drug or chemical modification of the cerebral environment is produced directly by introducing the substances into the arterial blood-supply to the brain by close-arterial injection — *i.e.*, into the carotid artery ipsilateral to the recording site.

The evoked potential method has enabled us to demonstrate (Fig. 3) that a dynamic equilibrium between excitatory neurohumoural agents like acetylcholine (Marrazzi 1953) and inhibitory ones like serotonin (Marazzi and Hart 1955) is built into the synaptic transmission system. As a part of normal function this equilibrium is transiently disturbed to transmit more impulses (excitation) or to transmit fewer impulses (inhibition). It is evident that such a system must be susceptible to modification by chemicals and drugs, and, indeed, it is. As suggested by the figure, the transmission process can conceivably be influenced in any of its segments — neurohumoural

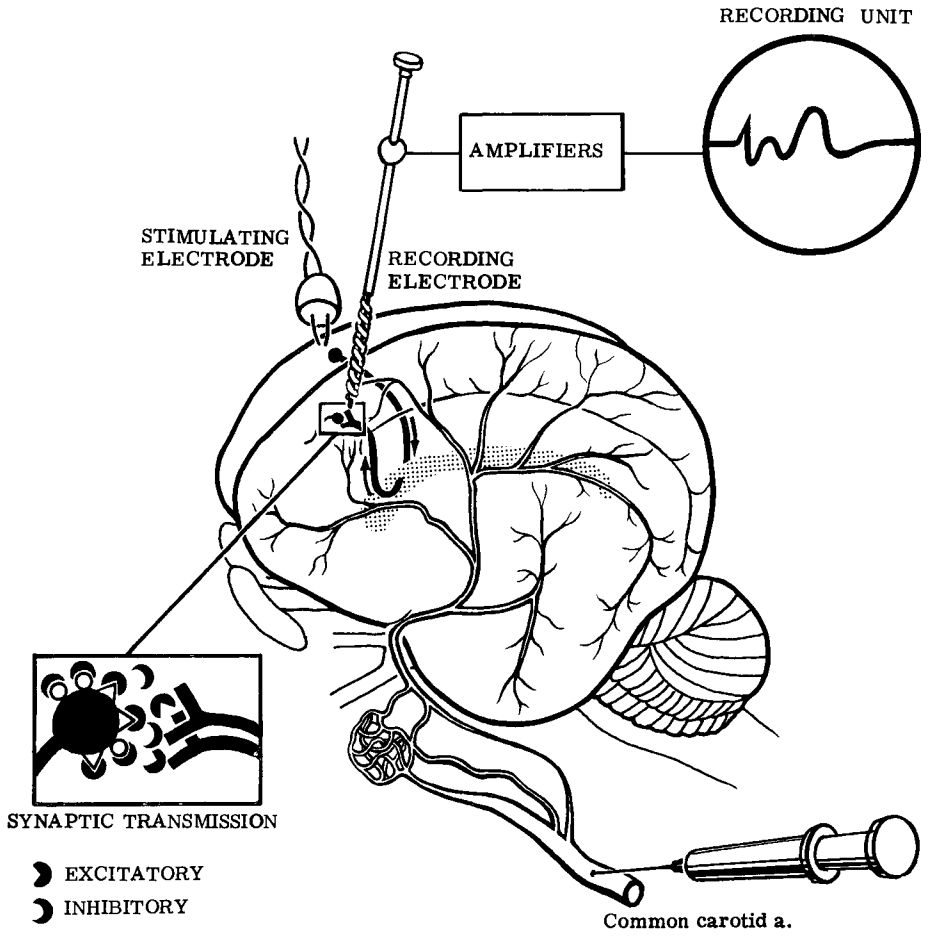


Fig. 2. Visualization of intercortical (trancallosal) pathway. Transparent cat brain with schematic arterial path to show ipsilateral distribution of common carotid injection.

liberation, destruction or alteration during migration across the synaptic gap, fixation to receptors and post-synaptic response. The last involves the metabolism of the post-synaptic neurone, while the others involve the metabolism of the transmission process.

We have been talking of effects that are properly regarded as primary because they are exhibited by the very cells upon which the drugs are acting. If we pass through an organisational system before recording the effects, we add more degrees of freedom and we have situations, such as in Figure 4, where we see that the *primary* effect may come through reinforced but unchanged in kind or, by passing through a suitable network, emerge as a *secondary* effect that is the opposite of the *primary*. For example, as shown on the right, *primary* inhibition may produce a *secondary* activation or release phenom-

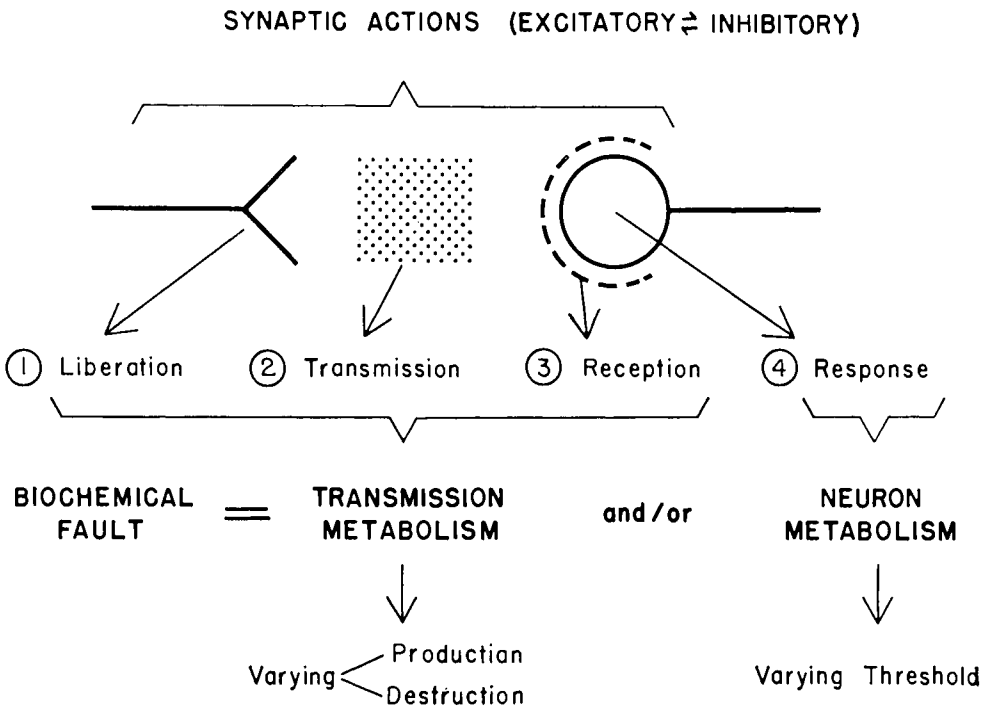


Fig. 3. Potential factors in disturbed synaptic equilibrium.

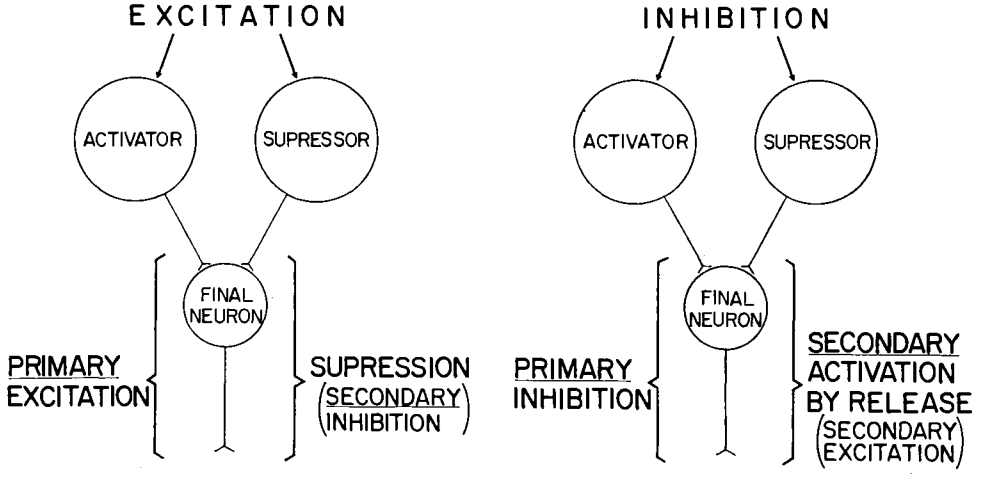


Fig. 4. Kinds of effect due to synaptic action.

enon, which cannot properly be called stimulation without confusion as to the true action of the drug at the beginning of the neuronal chain where it is taking place.

These diagrams apply to the problem of anticonvulsants; and theoretically it should be possible to manipulate therapeutically any one or more of the segments involved. However, the effective anticonvulsants all act by raising the threshold of the postsynaptic neurone and adjacent neurones involved in spread, by depressing the neurone or, in a few instances, by more specifically altering the ionic status and therefore the stability of the motor neurone cell membrane.

The Role of Gamma Aminobutyric Acid

It seems worth drawing attention to some of our recent work, because it offers the possibility of a new classification of anticonvulsants on an experimental basis. We have found (Marrazzi *et al.* 1958, Marrazzi 1960*b*) that gamma aminobutyric acid, a natural constituent of mammalian brain that is represented in the glutamic acid cycle, is a fairly potent cerebral synaptic inhibitor (Fig. 5). Since it was known that seizures experimentally induced by giving semicarbazides (Killam 1957) are associated with an interference with glutamic decarboxylase and a resulting fall in cerebral gamma aminobutyric acid, it seemed reasonable to examine the influence of clinically effective anticonvulsants on the cerebral synaptic inhibitory action of gamma aminobutyric acid.

In Figure 6 we see that Phenytoin (Dilantin R) prolongs the cerebral inhibitory action of gamma aminobutyric acid. Scrutinising the table of anticonvulsants (Fig. 7 Goodman and Gilman 1960) we see the beginning of an interesting correlation that may turn out to be of value in understanding convulsant disorders and in classifying convulsants. We tried a representative of each group in the table. Of these, Phenytoin, Phenacemide and the barbiturates prolonged the cerebral action of gamma aminobutyric acid, and Tridione did not. The suggestion is that gamma aminobutyric acid may, by exercising its inhibitory action, be one of the regulators of motor excitability. When it is deficient the anticonvulsants that prolong its effect would be expected to be corrective. The effectiveness of anticonvulsants that do not affect gamma aminobutyric acid implies that there are disturbances of motor excitability which are not contingent on this factor, and that this can be determined experimentally. Similarly, the technique can be used to determine whether anticonvulsants fall into this new category as well as whether manipulations of other parts of the glutamic acid cycle are practical in the design of a new anticonvulsant therapy.

Cerebral Synaptic Transmission and Behavioural State

One of the most interesting distortions of synaptic equilibrium is produced by the highly potent lysergic acid diethylamide (LSD-25) (Marrazzi and Hart 1955) (Fig. 8). This substance, by virtue of its ability to induce temporary and completely reversible mental derangement, is an invaluable experimental tool with an action very similar to that of serotonin, the cerebral inhibitory neurohumour. By thus creating an excess of cerebral synaptic inhibition, LSD-25 unbalances cerebral equilibrium — and the resulting failure of cerebral homeostasis manifests itself as mental disturbance.

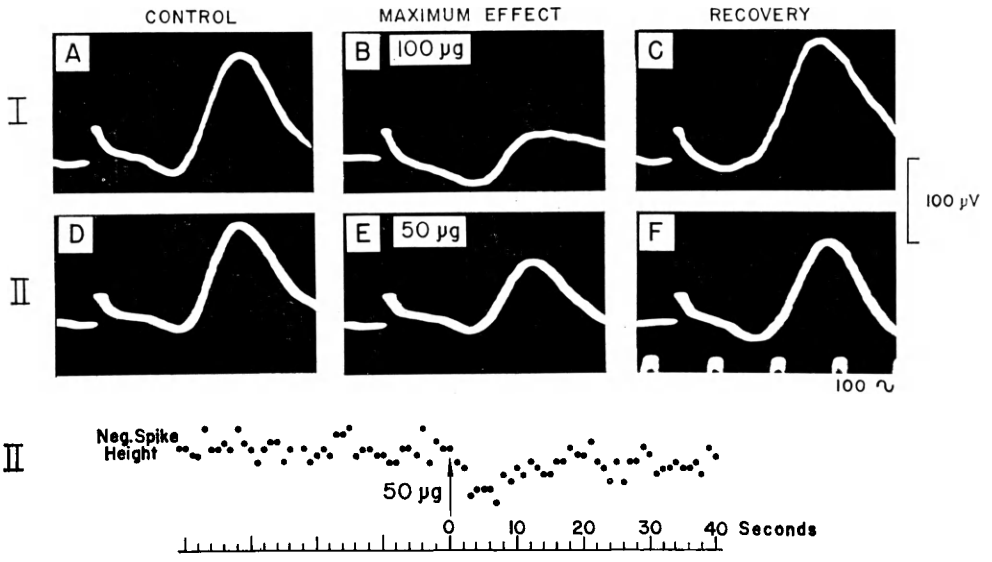


Fig. 5. Cerebral synaptic action of gamma aminobutyric acid in a 2-neurone intercortical (transcallosal) system. Potentials evoked in the cerebral cortex of the cat by electrical stimulation of the contralateral cortex every second. GABA injection into the ipsilateral common carotid.

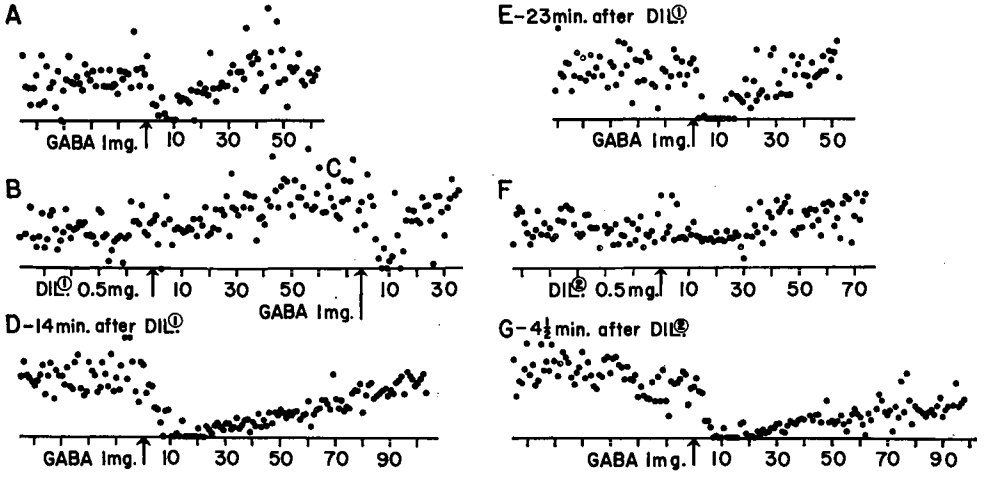
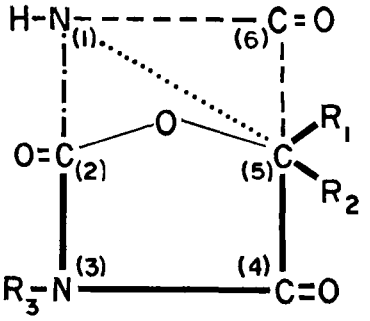


Fig. 6. Augmentation of GABA cerebral synaptic inhibition by dilantin. The dots represent negative cortical spike heights from transcallosal system potentials evoked by contralateral cortical stimulation (1 per second). Injections made into the common carotid.



Heavy line: Common denominator.

Dash line: Barbituric acid nucleus.

Dotted line: Hydantoin nucleus.

Thin line: Oxazolidine-2, 4-dione nucleus.

NUCLEUS AND DRUG	R_1	R_2	R_3	RELATIVE CLINICAL EFFICACY		
				Grand Mal	*Psychomotor*	*Petit Mal*[1] *Triad*
Barbituric Acid						
Phenobarbital	C_6H_5	C_2H_5	H	++++	0	+
Mephobarbital	C_6H_5	C_2H_5	CH_3	++++	0	+
Metharbital	C_2H_5	C_2H_5	CH_3	+++	0	(?)
Primidone[2]	C_6H_5	C_2H_5	H	+++	(?)	(?)
Hydantoin						
Diphenylhydantoin	C_6H_5	C_6H_5	H	++++	+++	0 or —
Mesantoin	C_6H_5	C_2H_5	CH_3	++++	+++	0 or —
Oxazolidine-2,4-Dione						
Trimethadione	CH_3	CH_3	CH_3	+	+	++++
Parathadione	C_2H_5	CH_3	CH_3	+	+	++
Straight-Chain Compounds						
Phenacemide[3]	C_6H_5	H	H	+	++++	+
Bromide[4]				+++	0	0 or —

[1] Includes pyknoepilepsy, myoclonus, and akinetic seizures. [2] Primidone differs from phenobarbital in having the area C:O replaced by CH_2. [3] Not a ring structure, but the compound can be viewed as a straight-chain analog of 5-phenyl hydantoin. [4] Bromide is included in chart for comparative purposes. Plus (+) signs indicate relative degree of benefit, 0 signifies no benefit. Minus (—) signs signify compound may aggrevate the disorder. (?) signifies claims made for the efficacy, but more data needed.

Figure 7. Relation of chemical structure of major antiepileptic drugs to their therapeutic efficacy.

Tranquilizers (in this case chlorpromazine — CPZ) act by preventing or reducing the action of LSD-25 (Fig. 8) (Marrazzi *et al.* 1963*a*, Marrazzi 1957). When the CPZ has been dissipated (3rd column, Fig. 8) LSD-25 can once more produce its original reduction of transmission, as indicated by the reduced postsynaptic evoked potential. The correspondence with the clinical situation is readily apparent.

Amphetamine has qualitatively the same type of action, so that it is in reality a cerebral synaptic inhibitor which sometimes, through inhibition of inhibition, elicits a release phenomenon that may be confused with true stimulation. Furthermore, we (Ray and Marrazzi 1961) have shown that tranquilizers are in fact weak synaptic inhibitors which exercise the desired effect by pre-empting the site of action and substituting their weak action for the stronger inhibiton to be offset. Therefore, it becomes clear that amphetamine and tranquilizers have related actions and it is only by appropriate dosage and skilful selection of cases that we can obtain suitable and apparently differing effects. I am here of course referring to the control of the hyperkinetic child

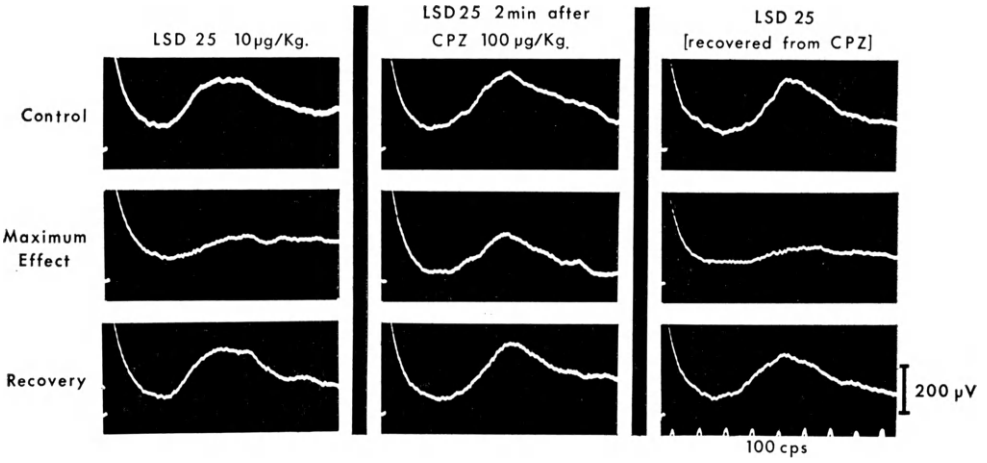


Fig. 8. Prevention of LSD 25 effect by chlorpromazine in an intercortical system. Potentials evoked in cerebral cortex of the cat by electrical stimulation every 2 seconds. Injection into the ipsilateral carotid artery.

by amphetamine and the emotionally disturbed one by tranquilizers, whereas amphetamine may make the latter group worse. In this connection I could call attention to amphetamine-induced psychosis and its higher incidence in Japan, where the use of amphetamine is so prevalent.

The action of amphetamine has long been associated with behavioural changes. When adequately quantitated and analysed these can be very instructive. For instance, Figure 9 shows the effects of increasing doses on 'decision making.' In this experiment a rat is trained to distinguish between two tones and can obtain a reward by pressing a lever when the correct tone is presented. By pressing another lever the rat can change the tone presented. In this way he can alternate between the two tones (or in the case of monkeys either between different coloured lights or between tones) until he makes up his mind. As seen in the control line, the rat performs this task quite easily, requiring only a few alterations. With a small dose of amphetamine there is little or no change in the number of errors, but this is associated with an almost tenfold increase in lever pressing (alternation). The true primary action that this increased activity reflects is inhibition and impediment in decision making. Larger doses increase the reaction time, eliminate the increase in alternation lever activity but increase the number of errors — signs associated with depression.

We have carried out this and many other behavioural experiments in laboratory animals (Marrazzi 1962*a*). Now, doing similar work in humans, I believe that this approach and the one to be described in studying perception will not only permit accurate estimation of clinical effectiveness but serve also as a practical means of assessing brain function and damage.

For convenience the examples of the pharmacology of the synapse have been selected from the studies on transcallosally activated cortical synapses. This has been permissible because (Fig. 10) all these effects have been obtained at cortical (Marrazzi 1961), subcortical (Marrazzi 1960*c*), brain stem reticular (Marrazzi *et al.* 1963) and medullary levels (Marrazzi 1953). The table testifies to the generality of cerebral

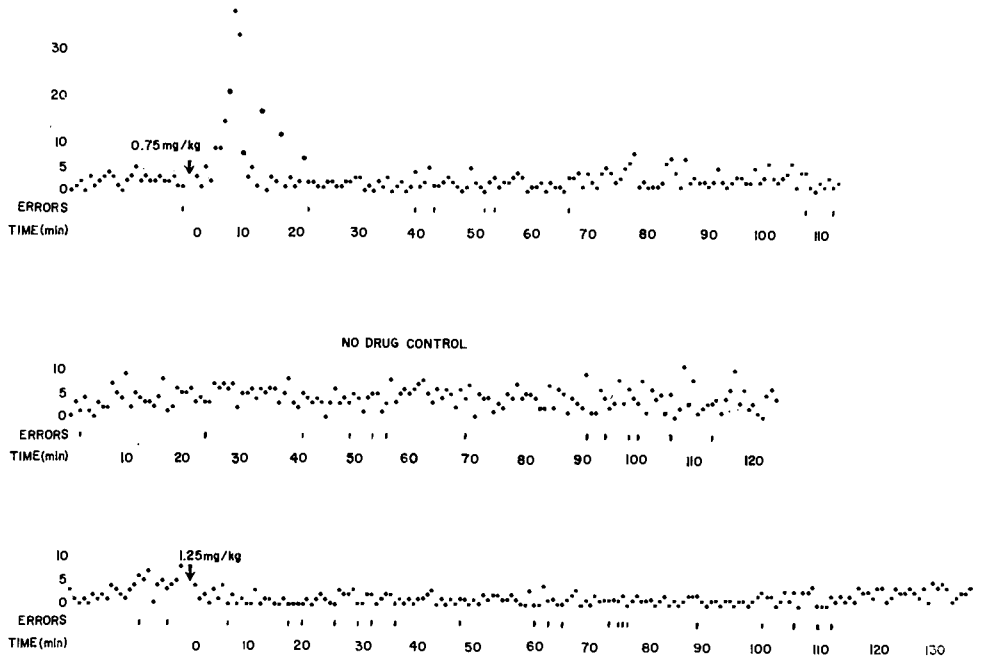


Fig. 9. Effect of a low and a moderate dose of amphetamine on stimulus selection behaviour in a 2-choice situation in a rat. The rate of lever pressing (absciassae) increases very considerably with the dose of 0.75 mg/k.

(1) Electrical recording methods in neurophysiological and neuropharmacological studies,

(2) Drugs as tools for analysis of mechanisms and for detailed comprehension of drug effects,

(3) Radioisotope tracer techniques,

(4) Neurochemical studies,

(5) Behavioral studies,

(6) Neurosurgical approaches in humans when otherwise clinically indicated,

(7) Clinical neuropharmacology,

(8) Correlation of experimental and clinical, (Experimental Psychiatry).

The **Veterans Administration Research Laboratories in Neuropsychiatry** will study basic mechanisms of neural, mental and behavioural function and their therapeutic alteration, by means of laboratory and clincial experimentation in animal and man. The methods to be employed are outlined above.

Figure 10

synaptic drug actions with differing patterns of activity due to the distribution of varying thresholds, rather than to the exercise of actions at limited specific sites. Raising the doses will elicit action through the full range of thresholds, the low threshold ones being the wanted actions and the high threshold ones regarded as toxic or unwanted actions.

Differential effects due to varying thresholds are in fact basic in understanding disturbed function in a system whose most distinguishing characteristic is integration. Direct cerebral recording with multiple electrodes reveals the manner and extent of the disintegrating or disrupting effect of LSD-25 and related drugs like amphetamine at the organisational and total levels.

In this way it is made evident that LSD-25 inhibition is exercised first on the association or memory areas of the cat. The resulting impediment in availability of information stored in the association areas, for comparison with the new information coming into the primary receiving areas, makes for inadequate reality checking or abnormal perception.

Thus, inadequate integration stands revealed as the basic dysfunction in mental disturbance — be it in childhood, adulthood, or senility; be it due to brain damage or to some endogenous psychotogen; be it a specific symptom, as in hallucination (Marrazzi 1962*b*) or be it the total syndrome, as in psychosis (Marrazzi *et al.* 1963).

Perception and Disturbed Cerebral Function

Aberrant perception is measurable, and we are devising ways of making it a 'clinical yardstick' for measuring disturbed cerebral function in any of its manifestations and in its response to any therapy. Our present way of conducting this test is illustrated in Figure 11. A visual illusion (this modality was chosen for convenience, others will eventually be used) is created by having the subject look into a five-sided room, whose outlines (cues) have been somewhat obscured by leaves, and then put on anisokonic lenses so that the binocular fusion of the disparate images so produced now results in a distorted room (Ames illusion — Ames 1961). By remote control the subject is asked to 'track' the apparent movement of the floor line by adjusting the guide bar, mounted in the middle of the back wall, to the same angle, *i.e.* to make it parallel with the floor, which now appears sloped. Because the illusion develops slowly and progressively, it is quite feasible to follow it in the manner described, arranging at the same time to graph the adjustment automatically. The adequacy of perceptual integration is now challenged by a tiny, subclinical dose of LSD-25, which produces no overt symptoms but whose effects are quantitatively expressed in the instrumentally obtained curve traced by the subject, who has acted as his own control in the pre-drug period of the session. Correlations are being developed between these data and the subject's clinical status, his response to therapy and the range of normal stable, normal unstable and mentally ill individuals.

Perceptual disorder is a well recognised factor in cerebral palsy but its accurate measurement proves difficult. I wish to propose that such a test as this, using amphetamine in place of LSD-25, be used to diagnose and objectively measure perceptual disorder and its response to therapy. Incidentally this correlation between such findings and

the efficacy of amphetamine in hyperkinetic children might provide a test of the potential value of this therapy in a particular case without the necessity of a full course of trial treatment.

Severe brain damage would manifest itself by an inter-area disintegration that could not be further modified by this kind of testing. Perhaps intermediate degrees of damage would require abnormally high doses of the challenging agent to produce modifications.

Such techniques could permit us to progress from opportune empiricism to rational exploration, utilizing objective criteria, such as perception and conditioned lever pressing in response to challenging chemicals and to therapies.

With adequate instrumentation involving electronic computers it is now possible to record evoked potentials from scalp electrodes, so that direct input and output correlations could be used to bring to the clinic the kind of analysis that is now only possible in the experimental laboratory. Instrumental complexity can, as in this case, lead to conceptual simplification. Fig. 12 draws attention to the effects of the only two possible modifications in cell function— namely, increase or excitation and decrease or inhibition. The chart has been drawn to emphasise the similarity of all inhibitors and of all excitors. It is surely a worthwhile simplification if we realise that all inhibitors and excitors can be made to exhibit all the respective effects charted and that the continuity is merely a function of dose. Such clinical terms as sedatives, convulsants, antispasmodics, tranquilizers and anaesthetics reflect the dose range for the spectrum of action of that particular drug which we find useful. This dose range in a useful drug is such that one rarely gets effects from extension of the action of the drug into undesirable parts of that spectrum.

Conclusions

We have touched on several aspects of the behavioural problem, but the main one, that of difficulty in maturation, both inherent and — often largely or only — as a consequence of frustrating encounters with the world because of handicaps, looms large. One would wish to supply better aid to the skilled care that now has to rely almost entirely on patience and devotion. Perhaps it is an important step to realise that in this, as in any disturbance of an adaptive system, it is necessary not only to remove the cause, which is rarely possible, and to strengthen adaptive behaviour, but to extinguish maladaptive behaviour as well. Beyond general stimulation and the reduction of inhibitions, one hopes for more specific drug effects on learning.

These are not yet available and will not come easily; but it is not too far-fetched to hope that studies of the possible molecular encoding or memory mechanisms by sophisticated interdisciplinary studies, correlating neuronal RNA with quantified behavioural, neurophysiological and neuropharmacological aspects of learning, will provide the means of accelerating the metabolism of learning and perhaps even of removing the dead wood of unwanted and now useless accruals.

It may be rewarding to include this in the efforts to alleviate or correct metabolic deviations such as the phenylketonuria and galactosaemia that are now being thoroughly studied.

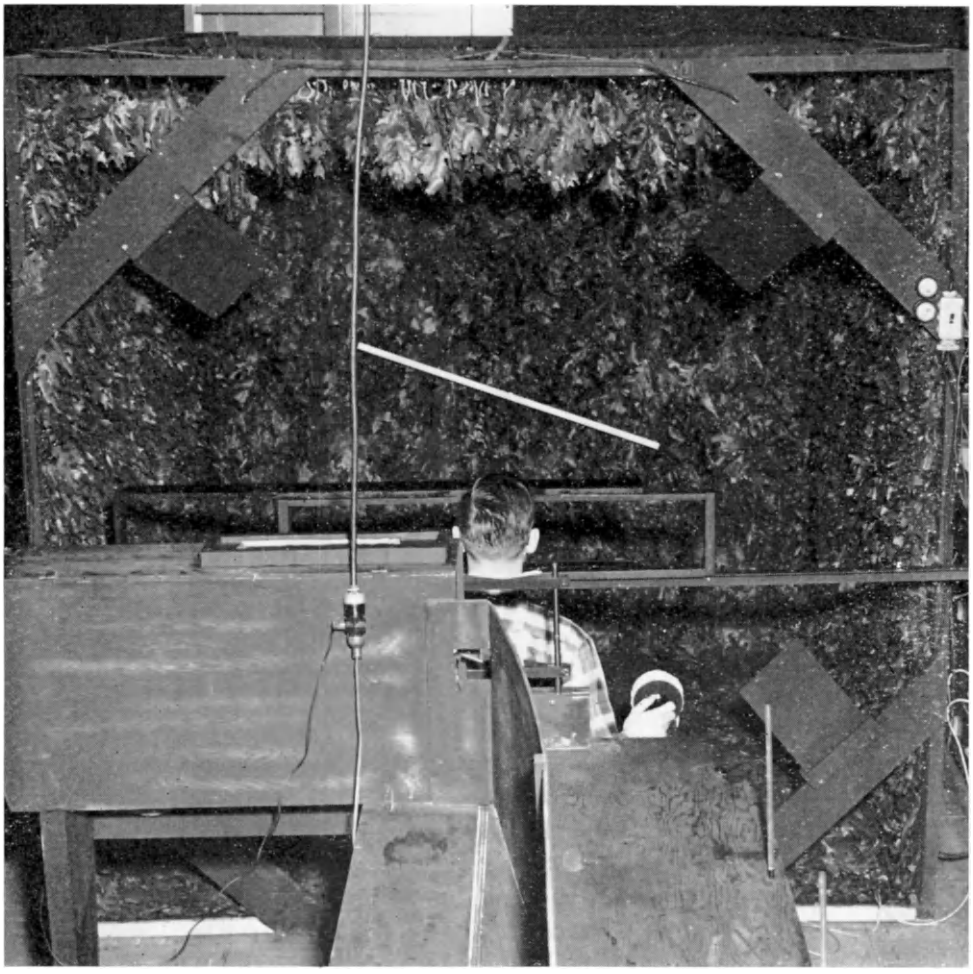


Fig. 11. The Ames illusion. For explanation see text.

Without going further afield let me summarise by saying that the outlook based on potential new approaches can be regarded optimistically. Cerebral dysfunction of any sort may be regarded as a failure of homeostasis and its consequences (Fig. 1).

Our findings are summarised below (Marrazzi 1963). If the relevant counterparts in cerebral palsy are substituted, this summary is an expression of what I believe can be done by any group willing to make the much needed and rewarding investment.

Outlook

The experimental approach has improved the outlook.
The laboratories have contributed:

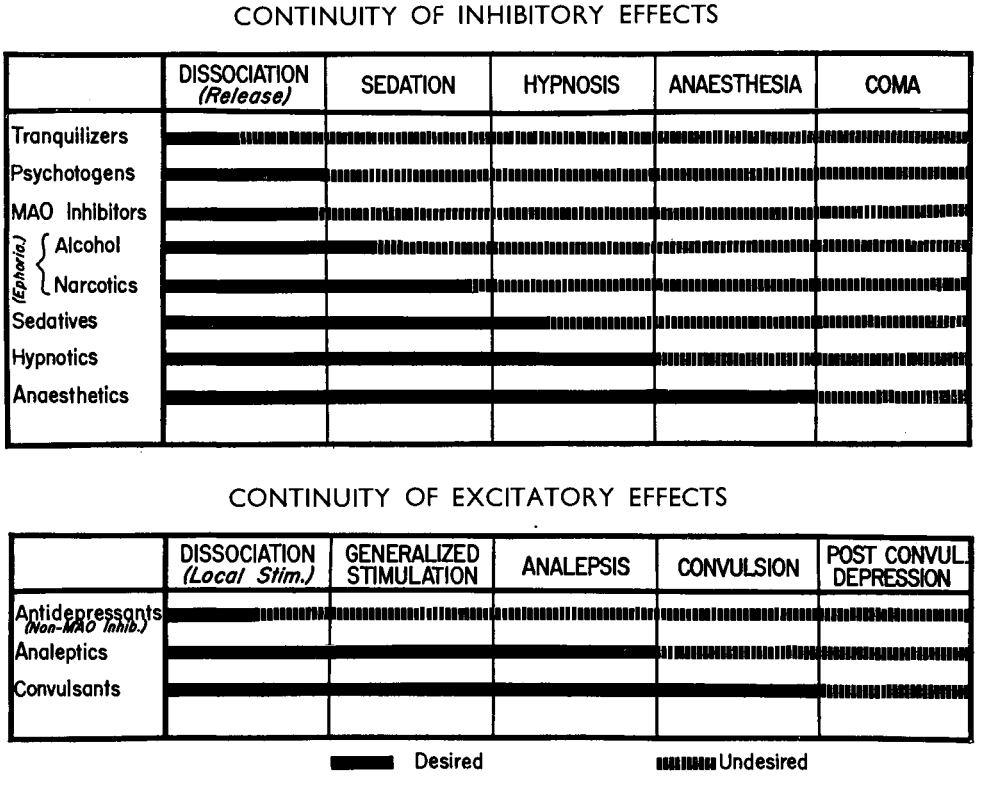


Fig. 12. A chart demonstrating the relationship between inhibitors and excitors.

1. A detailed mechanism of cerebral synaptic transmission and its dynamic equilibrium,
2. A mechanism of psychotogen action,
3. Extraction of a psychotogenic small molecule from blood,
4. A mechanism of tranquilizer action,
5. A partial mechanism of antidepressant action,
6. A concept of hallucination,
7. A concept of psychosis,
8. A framework of cerebral homeostasis to contain and explain all of these,
9. The application of the foregoing to the development of clinical yardsticks and to the improvement of therapy.

REFERENCES

Ames, A. Jr. (1961) 'Anisokonic glasses.' *In* Explorations in Transactional Psychology, ed. by F. P. Kilpatrick. New York: New York University Press.

Denhoff, E., Robinault, I. (1960) Cerebral Palsy and Related Disorders. A Developmental Approach to Dysfunction. New York: McGraw Hill.

Goodman, S., Gilman, A. (1960) The Pharmacological Basis of Therapeutics. New York: Macmillan.

Killam, K. F. (1957) 'Convulsant hydrazides II. Comparison of electrical changes and enzyme inhibition induced by the administration of thiosemicarbazide.' *J. Pharmacol. exp. Ther.* **119,** 263.
Marrazzi, A. S. (1953) 'Some indications of cerebral humoral mechanisms.' *Science,* **118,** 367.
—— (1957) 'The effects of certain drugs on cerebral synapses.' *Ann. N.Y. Acad. Sci.,* **66,** 496.
—— (1960*a*) 'Methodological problems in neuropharmacologic research.' *In* Recent Advances in Biological Psychiatry, ed. by J. Wortis. New York: Grune & Stratton, vol. II, p. 379.
—— (1960*b*) 'Round table on significance of gamma aminobutyric acid (GABA) in the brain.' *In* Recent Advances in Biological Psychiatry, *op.cit.*, p.70.
—— (1960*c*) 'The action of psychotogens and a neurophysiological theory of hallucination,' *Amer. J. Psychiat.*, **116,** 911.
—— (1961) 'Inhibition as a determinant of synaptic and behavioral patterns.' *Ann. N.Y. Acad. Sci.,* **92,** 990.
—— (1962*a*) 'Synaptic and behavioral correlates of psychotherapeutic and related drug actions.' *Ann. N.Y. Acad. Sci.,* **96,** 211.
—— (1962*b*) 'Pharmacodynamics of hallucinations.' *In* Hallucinations, APA-AAAS Symposium on Hallucinations, ed. by L. J. West. New York: Grune & Stratton.
—— (1963) Veterans Administration Research Laboratories in Neuropsychiatry. Report of the Seventh Year. Pittsburgh.
—— Chalmers, R. K., Hart, E. R. (1963*b*) 'Do psychotogens and tranquilizers have special brainstem actions?' *Amer. J. Psychiat.,* **120,** 762.
—— Hart, E. R. (1955*a*) 'Relationship of hallucinogens to adrenergic cerebral neurohumors.' *Science,* **121,** 365.
—— —— (1955*b*) 'The possible role of inhibition at adrenergic synapses in the mechanism of hallucinogenic and related drug actions.' *J. nerv. ment. Dis.,* **122,** 453.
—— —— Ray, O. S. (1963*a*) 'Cerebral homeostasis, dysfunction, and psychosis.' *In* Recent Advances in Biological Psychiatry, *op. cit.*, vol V, p. 309.
—— —— Rodriguez, J. M. (1958) 'Action of blood-borne gamma-aminobutyric acid on central synapses.' *Science,* **127,** 284.
Ray, O. S., Marrazzi, A. S. (1961) 'A quantifiable behavioral correlate of psychotogen and tranquilizer actions.' *Science,* **133,** 1705.

CHAPTER 4

The History of Drug Therapy in Cerebral Palsy

MEYER PERLSTEIN

Life is short and art is long; the occasion fleeting; experience fallacious and judgement difficult. (Aphorism of Hippocrates)

The desire to take medicine is perhaps the greatest feature which distinguishes men from animals. (William Osler)

From ancient time to the present day, man has been absorbed in a constant search for drugs to alleviate and eliminate disease. Starting with incantations, diet, herbs and concoctions which were used to treat all illnesses, he is now able to aim drug therapy at specific organisms, chemical deficiencies and physiological mechanisms, with notable successes in certain areas and failures in others.

While the 'magic bullet' to cure cerebral palsy has not yet been found, many neurologic conditions have responded gratifyingly to specific drugs—for example, the epilepsies, myasthenia gravis, Parkinsonism, certain psychiatric disorders, and some of the hyperkinetic postencephalitic syndromes. Consequently, drug therapy has been successful in alleviating many of the symptoms associated with cerebral palsy, such as convulsions, nutritional deficiencies, and some emotional and behavioral problems.

However, when someone speaks of the 'specific' drug therapy of cerebral palsy, he is usually referring to improvement in muscle tone and voluntary movement by pharmacologic agents acting on neurophysiologic mechanisms concerned with motor function. Since cerebral palsy is not a single disease, but a combination of many syndromes, it is obvious that no single drug can be expected to correct the pathologic physiology of all types of motor defects. Some drugs might increase and others decrease muscle tone; some might specifically control either tremors or athetosis, others rigidity or spasticity, since each of these motor aberrations is presumably based upon a specific and different neurologic lesion. Until more is known about the pathogenesis and neurophysiology of cerebral palsy, it is therefore not likely that a single specific drug will be found, except by serendipity, to correct all the motor defects of this condition.

One of the difficulties in measuring motor improvement due to drugs in cerebral palsy is the paucity of good methods of measuring motor performance and progress. It is difficult to construct a controlled method of examination that will eliminate the effects of growth, development, motivation and emotional synergies. Of course, motor function in cerebral palsy may clinically be improved following amelioration of some of the secondary, or associated symptoms, but usually this improvement is psychosomatic, coming from increased motivation, reduced frustration or elimination of emotional triggers, or it may be entirely a placebo effect. Such results may often be duplicated by non-pharmacologic means — *e.g.*, hypnosis, psychiatric management, or placebos.

A drug given for its specific action either as an anti-epileptic, or as a tranquilizer, may be effective in both areas and may also improve motor function. For instance, sodium hydantoin (Dilantin R), given as an anticonvulsant, might also control psychomotor or behavioural difficulties of epileptic origin. It might also improve or eliminate subclinical epileptic episodes responsible for school or learning difficulties, and thus decrease frustration and tension, and secondarily improve motor ability.* Meprobamate is not only a tranquilizer, but also has an anti-petit mal action, and, in addition, might be expected to affect motor function by its specific inhibition of polysynaptic irradiation.

Anti-epileptic Drugs and Sedatives

The modern drug therapy of cerebral palsy began with the use of sedatives and anti-epileptic drugs. Starting with bromides, the drug therapy of cerebral palsy has run the gamut of barbiturates and other sedatives. Some sedatives, and particularly the barbiturates, were found to exert a paradoxical or exciting effect with aggravated motor function and behavior in many patients with cerebral palsy. At other times, the soporific effect of the drug overshadowed its possible beneficial effects. When these drugs did improve motor function, it is doubtful whether the improvement was due to pharmacologic correction of a neurophysiologic motor abnormality, or to an anti-epileptic or tranquilizing effect.

The search continued for drugs that would reduce emotional tensions without causing drowsiness. A multitude of ineffective sedatives appeared on the market. Most of these were analgesics and/or antihistaminic drugs with a mild sedative action, and some were so mild that they could be bought without a prescription. Credit must be given to the ingenuity of the pharmaceutical ad. writers who described these drugs, not as ineffective sedatives, but as 'daytime sedatives.' An occasional cerebral palsied patient was helped by these drugs, probably by reduction of emotional tension or by suggestion, a result easily duplicated by placebos.

One of the best tension relievers, well known to the ancients, is spiritus frumenti in the form of alcoholic libations. Imbibed alcohol was long ago found to be effective in improving motor function in the cerebral palsied. Dr. Earl Carlson (1941) was one of the advocates of this drug for reducing tension and thus improving voluntary movement. The actual manner in which alcohol has its effect is not known, although it is presumed that it is mainly on the cortical and subcortical centers, rather than on the gamma system. However, this is known — that alcohol is still one of the best and safest tranquilizers available and acts just as well in cerebral palsy as it does in the normal population to reduce tension. Although its consumption may be associated with decreased motor skills in the normal person, it often (unless given to the point

*There is no corroboration for Kabat's statement (1959) that the improvement in athetosis which may follow Dilantin therapy is due to a specific effect of the drug on athetosis. He postulates that athetosis is due to cerebellar overaction caused by removing antagonisms of the basal nuclei. Dilantin presumably improves the athetosis by decreasing cerebellar activity. Conversely, he suggests that the phenothiazines, in addition to their psychopharmacological effects, also have a specific action in improving ataxia. Ataxia, he postulates, is due to basal nuclear overaction, due to the removal of cerebellar inhibitory influences. Phenothiazines, by depressing basal nuclear activity short of causing 'extrapyramidal' symptoms, would thus decrease ataxia. These speculations, although interesting, have not been corroborated.

of inebriation) improves the motor ability of the cerebral palsied. This property is not unique to alcohol. Similar improvement may follow general anesthesia with ether or other inhalants. Even carbon dioxide, given to the point of unconsciousness, was shown by Fay (1953) to improve athetosis. Fay believed that only CO_2, by increasing brain blood flow, had specific ability to improve athetosis, but nitrous oxide and many other gases may often do the same, provided they are given to the point of unconsciousness.

Drugs Specifically Affecting Neuro-muscular Disorders

After the 1918 influenza epidemic, when it was found that drugs related to the nightshade group, such as belladonna, atropine and stramonium, had specific effects in decreasing rigidity and tremors, it was natural to try them with the cerebral palsied. These drugs were found to be occasionally beneficial, primarily in patients with extrapyramidal syndromes, such as tremors and cogwheel rigidity. The synthetic anti-parkinson drugs, such as trihexyphenidyl (Artane R), cycrimine hydrochloride (Pagitane R), and procyclidine hydrochloride (Kemadrin R) have replaced to a great extent the natural drugs with equal, but limited benefit for the patient with cerebral palsy. The total number of cerebral palsied patients helped by these drugs is relatively small.

Drugs acting on myoneural or synaptic mechanisms were first used primarily to change muscle tone. Quinine and procaine amide, found useful in reducing the myotonic state in myotonia dystrophica, were unsuccessful in cerebral palsy. Strychnine, on the other hand, acting on spinal synapses, did increase muscle tone in the hypotonic cerebral palsied patient, but the relatively small improvement in motor ability was too high a price to pay for the real danger of strychnine-induced seizures.

Curare, acting on the myoneural junction, was theoretically an ideal drug, since it decreased muscle tension to the point of paralysis. The therapeutic index was so low, however, that either respiratory paralytic or non-effective dosages were frequently given. Moreover, it had to be given by injection, which created problems of sterile abscesses and painful experiences. When given in aqueous solution, the length of action of the drug was transitory. When given in long-acting or depot form it was generally ineffective. Although the drug had theoretical benefits as based on laboratory experiments, it was not the clinical solution to the problem, as is evidenced by the fact that it is now rarely used.

One of the paradoxes in the history of drug therapy in cerebral palsy is that when curare did not work, its antagonist, neostigmine, was tried. The same drug used to increase strength in myasthenia gravis was recommended to reduce muscle tone in the tense cerebral palsied patient. The theoretical basis for the use of neostigmine was the finding that in animals it would cause muscle relaxation, presumably due to enhancement of inhibitory impulse transmission. Double-blind studies in patients with this drug, however, indicated that its benefit was no greater than that of a placebo and that the occasional benefit attributed to it might actually have come from atropine, which was often given along with it as an antidote for its cholinergic effects (Perlstein 1950). In the Russian literature, galanthamine, an alkaloid cholinesterase inhibitor, has been reported as giving excellent results in cerebral palsy. It is doubtful that this drug will be of greater value than neostigmine or its analogues.

Muscle Relaxants

In the last ten years, the trend has been towards the 'muscle relaxant' drugs, starting with mephenesin (Tolserol R) and its derivatives—*e.g.* diethylpropanediol (Prenderol R), meprobamate (Miltown R), and later, carisoprodol (Soma R). These were followed by a number of other drugs chemically related or with a similar neurophysiologic action in reducing the polysynaptic irradiation of impulses.*

From a theoretical viewpoint, it would be logical to believe that such drugs might effectively reduce spasticity. Although a monosynaptic reflex such as is the knee-jerk would not be affected, the irradiation of this reflex to antagonistic and synergic muscle groups should be reduced or eliminated. Such an effect can, in fact, be demonstrated electro-myographically in the cerebral palsied patient. One would therefore expect these drugs to be more effective in spastics, in whom the irradiation from a local stimulus might evoke mass reflexes. However, in most reports on the benefits of muscle relaxants, athetoids are helped more than spastics. Athetoids are known to have aggravation or improvement of their motor difficulties depending upon the presence or absence of emotional stress. The emotional stresses of puberty and the menopause often result in 'pseudoprogression' of athetosis. Obviously, then, the main action of the 'muscle relaxant' drug has not been due to its physiologic action in reducing polysynaptic transmissions, but to some other effect. This 'other effect' is similar to that seen with any tranquilizer or sedative — namely, a reduction of emotional tension. Most of the muscle relaxants are known to have such central tranquilizing or sedating action. It is of interest that many of the tranquilizing drugs may help not only tensions of the cerebral palsied, but also other clinical syndromes which may be triggered by emotional factors—*e.g.*, petit mal and allergic episodes.

When the phenothiazine and related psychotherapeutic drugs became available, it was natural that they, too, should be tried in cerebral palsy. Starting with chlorpromazine (Thorazine R), practically every phenothiazine derivative has been used, and in most instances some glowing reports of their efficacy in cerebral palsy were published. The same has been true of other drugs with neuropsychiatric action—*e.g.*, chlordiazepoxide (Librium R) and diazepam (Valium R). In many of these, a relaxant muscle effect by decreasing spinal or reticular polysynaptic irradiation can be demonstrated. Yet, in practically all, the reported beneficial effects have been mainly in athetoids, indicating that it may be the control of the emotional trigger rather than a correction of a motor abnormality that is beneficial. It is characteristic of such drugs that the benefits are not lasting, but 'wear off' as 'the patient becomes used to the medicine.' Often the improvement is proportionate to the confidence the giver of the drug has in its efficacy, and his ability to transmit this enthusiastic faith to the patient.

Each new drug has been introduced with a flow of literature describing optimistic specific and at times almost miraculous curative powers. Most of these reports were by competent, experienced and thoroughly honest physicians. They were often followed by more conservative reports which emanated from double-blind studies and which indicated that practically all of these drugs were no more effective than placebos.

*Among the drugs employed were zoxalzamine (Flexin), since removed from the market, methocarbamol (Robaxin), phenyramidol HCl (Analexin), metaxalone (Skelaxin), hydroxyzine HCl (Atarax), orphenadrine citrate (Norflex), styramate (Sinaxar), chlormezanone (Trancopal), to name a few.

The double-blind technique is the only way to differentiate the motor from the psychologic or sedating effect of a drug. If in the preliminary trials with a drug no benefit is observed, there is no need to use the double-blind technique; but if it does help, then the degree or the nature of its efficacy can be delineated only by a double-blind study, a difficult, expensive and time-consuming procedure. Unfortunately, most drug studies have been not double-blind but myopic.

The Cerebral Palsied Patient and Drug Therapy

Patients with lingering illnesses, such as arthritis, chronic skin or pulmonic diseases, or many neurologic disorders, often fall prey to charlatans and quacks who make pretentious and roseate, though unsubstantiated, claims for their nostrums, fads and wonder drugs. These claims may sometimes unwittingly be aided and abetted by the lay press, which, in its attempt to publicize medical advances, may extol some of the miraculous cures wrought by certain new drugs. Small wonder, then, that patients and parents often exert well-meant pressures on doctors to 'do something' by using some of these propagandized drugs, and that doctors, having nothing better to offer, may decide to prescribe them if only for their placebo effect on patient and parent.

One must bear in mind that, in cerebral palsy, drugs are only an adjuvant or incomplete part of the total therapy programme and that there is a limit to what can be expected from drugs alone. Even the drugs with the greatest alleged benefits help only 20 per cent to 30 per cent of the patients in the most optimistic reports. This can also be said of any method of therapy.

The history of drug therapy is comparable to that of physical therapy, in which numerous 'systems' have been devised and advocated by honest and competent individuals, who, through their personalities, have actually achieved good results. It is of interest that the same good results are achieved by conflicting 'systems.' This of course, is the secret of the placebo effect. If a drug is harmless, or without serious side effects, there is no reason to decry its use, even if only for a placebo effect. However, if there are toxic or unpleasant side effects one should never make the treatment worse than the disease.

In spite of the absence to date of a specific drug for cerebral palsy, the search does and should continue. The ideal drug would be one that would normalize tone and eliminate extraneous and involuntary motion while not interfering with voluntary motion. The closest we have come to this has been locally injected novocaine, which, by its action on muscle spindles, gives a temporary removal of spasticity without interfering with voluntary motion. No oral drug with a sustained similar action is yet available.

The future of the drug therapy of cerebral palsy will depend upon more basic studies and knowledge of the mechanisms responsible for muscle tone and for control of voluntary motion. There is a need for rationalization, for a theoretical approach on which to base the search for new drugs, but there is also a need for sober empiricism and clinical experience to make the difficult judgement as to whether a given drug truly fulfils its theoretical requirements.

CHAPTER 5

Recording the Progress of Skills in Cerebral Palsy

WINTHROP PHELPS

There are two aspects of drug evaluation in cerebral palsy.

One is the determination of the immediate or direct effects of the drug on patients, and these are measured in various ways. Electromyographic records can be made on muscles or pairs of muscles, and chemical changes in muscles and nerve conductivity are also measurable. Peripheral sensory changes can be determined by neurological techniques, and the effects of drugs on alertness, speed of reflexes and other psychological manifestations are easily studied. This type of drug evaluation, in the laboratory and on the patient, is necessary and valuable, but when all the findings are grouped together the resultant picture may still not cover the total effect on the patient's abilities.

The second is the double-blind test, used widely in clinical evaluation.

Some method is needed, however, to record the results. The use of films, at slow and normal speeds, is good for demonstration and for teaching purposes, but proves impracticable for long-term recording. I tried using film twenty-five years ago. A fifteen-minute film was taken every three months for a period of five years covering certain specific activities of each of twenty patients. At the end of the five years there were five hours of film on each patient, and the total time needed to review the twenty was one hundred hours.

I first used graphs in 1937 when the Children's Rehabilitation Institute was opened near Baltimore (Phelps 1941). Since then continuous graphs have been kept on all patients as long as they are at the Institute. Six or eight graphs in the different fields of treatment are maintained on all patients, and some cover several years. The advantage of this method is that the patient's improvement can be seen at a glance and treatment regulated accordingly. The graph serves as a base line, and if treatment is effective the rise in the graph must be sharper than the angle of normal maturation. A base line without treatment or medication must therefore be established first.

Hundreds of activities can be graphed in physiotherapy, occupational therapy and speech therapy. The graphs are measured against time and distance, and they are recorded once a week. Accurately measured distances and stop watches are used to evaluate speed of walking, size of steps, *etc.* Lists of activities studied in this way at the Children's Rehabilitation Centre are given as an appendix to this paper.

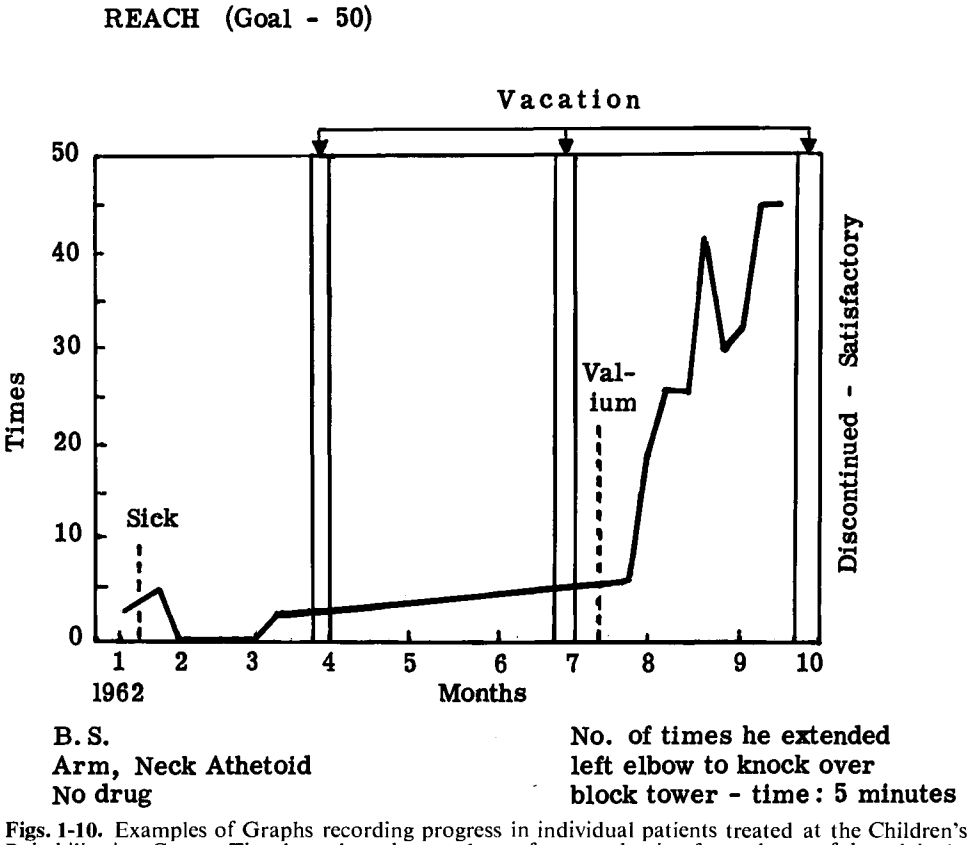
Figures 1-10 show the results of the different therapies. In the second medication has been added. In some instances the nature of the medicine is known to the therapist, while in others it is not. Most of the patients are children who take medication of various sorts continuously, such as vitamins and anti-convulsants, and the addition

of another is not particularly noticed. Since the measurements are against time and distance there is no subjective evaluation by therapist or patient, and because the graphing is done weekly the patient becomes so used to it that his performance is standardised. The graphs are shown to some of the older children to stimulate their interest and pride in accomplishment. This is obviously not necessary with the younger group. When a graph fails to show progress, the indication is that the particular treatment method or drug is ineffective and should be changed. At other times failure may show that the child is 'stale' for that particular treatment or that he is below par physically. These possibilties can then be followed up.

The method of recording by graphs requires a thoroughly trained staff. The items to be graphed depend on the aims of treatment in each patient. Time must not be wasted in pursuing one method with a child only to find that it is not applicable. In this way the most effective programme can be determined in all fields and the maximal speed of improvement attained.

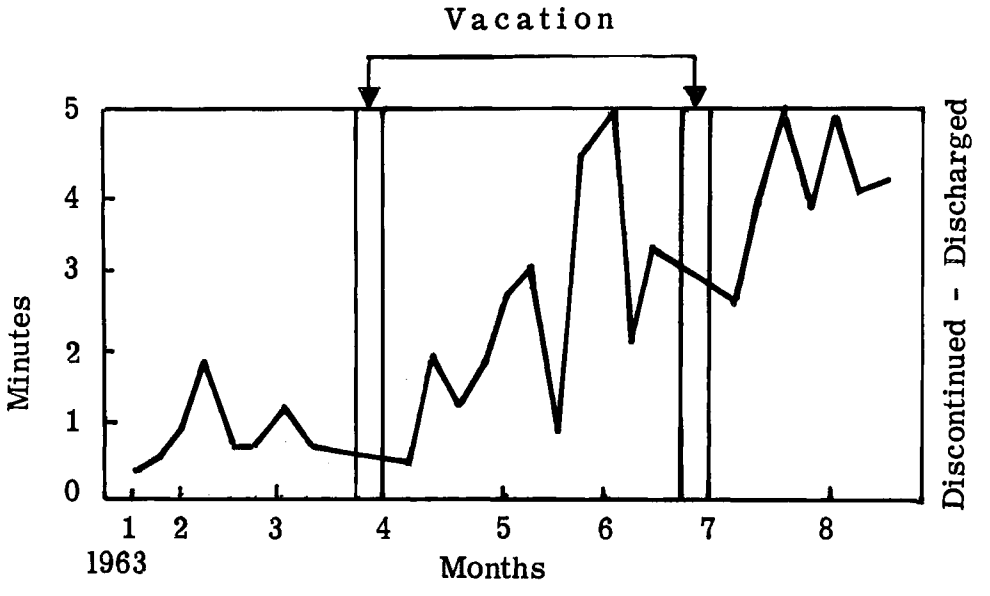
REFERENCE

Phelps, W. (1941) 'Evidences of improvement in athetosis treated by re-education.' *Res. Publ. Ass. nerv. ment. Dis.*, **21**, 529.



Figs. 1-10. Examples of Graphs recording progress in individual patients treated at the Children's Rehabilitation Centre. The charts have been redrawn for reproduction from photos of the originals.

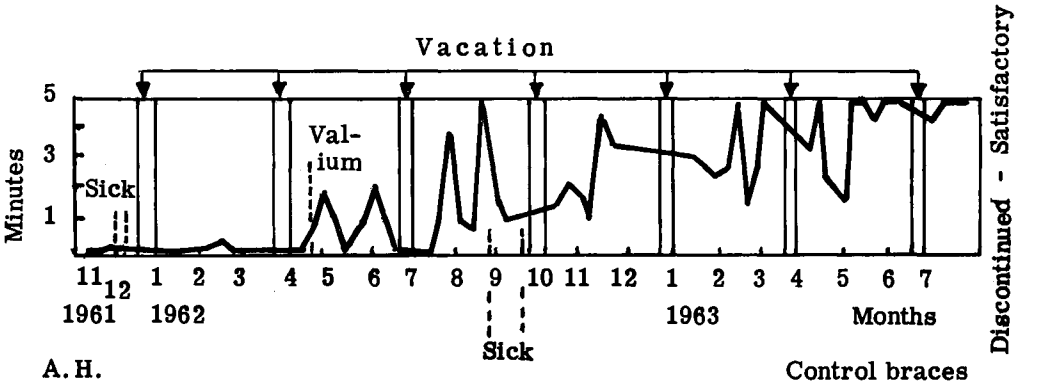
STANDING BALANCE (Goal - 5 minutes)



M. S.
Ataxic
No drug

Short leg braces
Weighted cuffs on legs

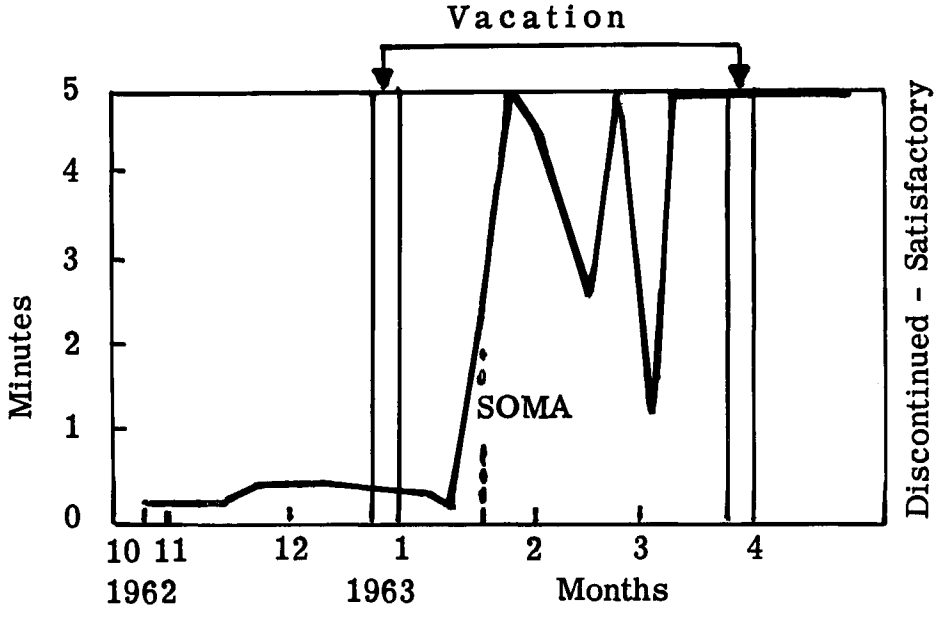
STANDING BALANCE (Goal - 5 minutes)



A. H.
Rotary Athetoid
No drug

Control braces
Skis

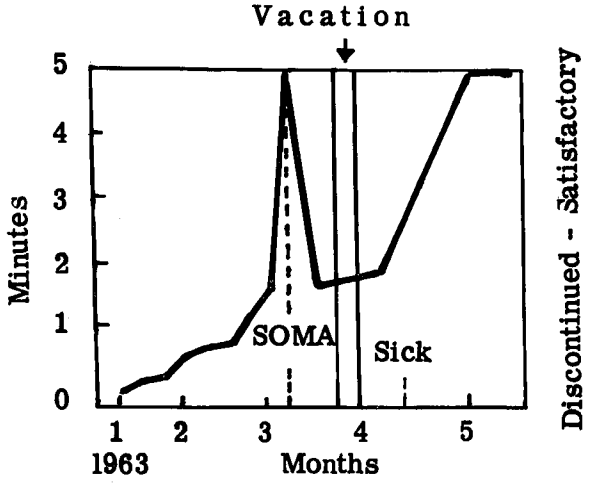
STANDING BALANCE (Goal 5 minutes)



S. B.
Spastic Quad.
No drug

Control Braces
Skis

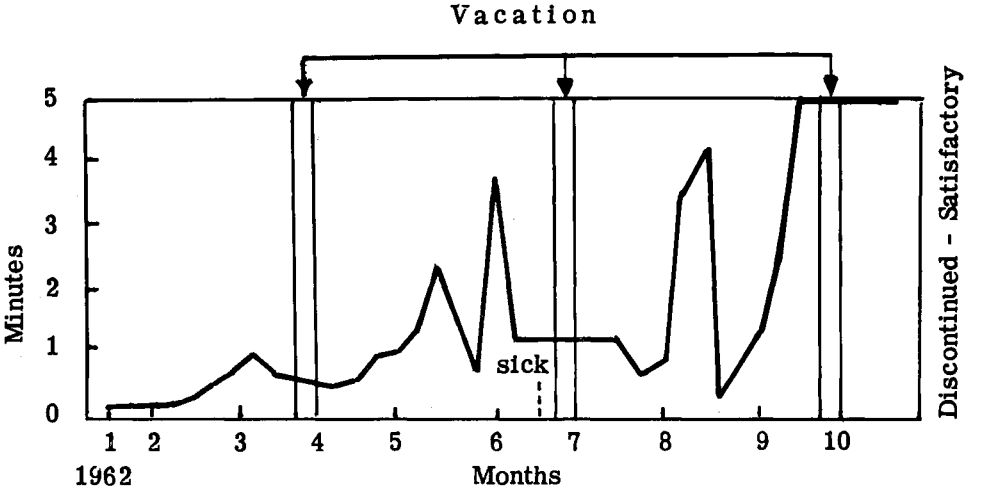
STANDING BALANCE (Goal - 5 minutes)



L. M.
Spastic Paraplegia
No drug

Using skis

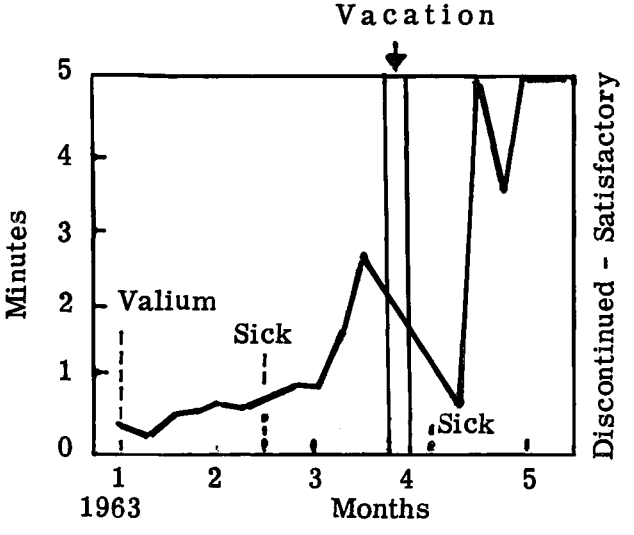
STANDING BALANCE (Goal - 5 minutes)



S. B.
Spastic Quad.
No drug

Control braces - locked knees
Stabilizer
Support at knees

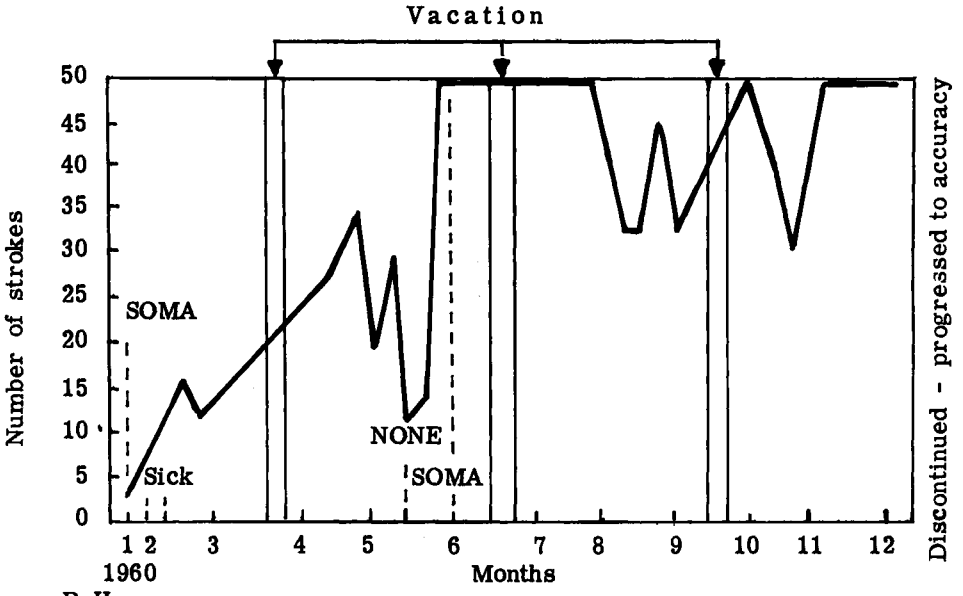
STANDING BALANCE (Goal - 5 minutes)



J. K.
Rotary Athetoid
Drug : Valium

Using skis
Wearing control braces

PRE-TYPING (Goal - 60 strokes)



B. H.
Intermittent rigidity

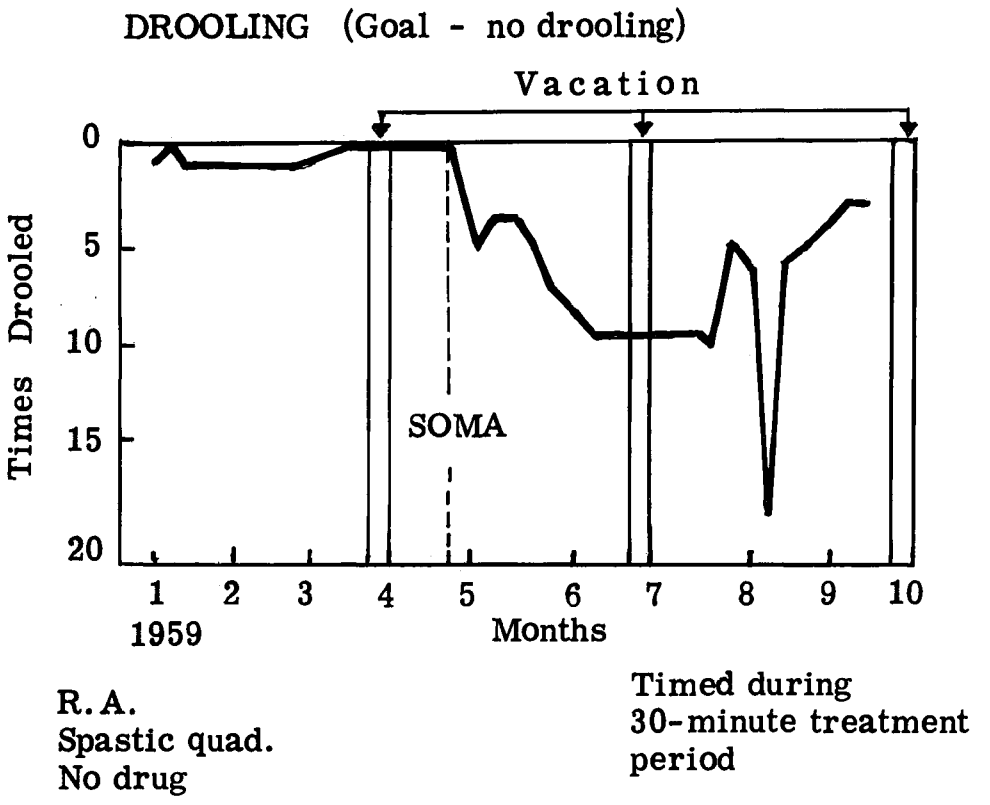
Greatest number of consecutive strokes - random keys
electric typewriter - shield
mouth stick
both hands cuffed

Appendix

The following are the lists used at the Children's Rehabilitation Institute to record progress and assess therapy in the various different areas of the patients' activities.

Graphs being used for Physical Therapy

Graph Titles	*Goal*	*Procedure*
Head control	time for 5 min goal — 5 min.	Length of time child can hold head upright without support.
Sitting balance	time for 5 min. goal — 5 min.	Length of time child can sit. Indicate type of support — sand bags, braces etc.
Standing balance	time for 5 min. goal — 5 min.	Length of time child can stand. Indicate type of support — stabilizer, skis, extended heels etc.
Walking speed	time for 4 min. goal — 10 sec.	Length of time to walk 15 feet. Indicate type of brace and any apparatus such as canes, tripod crutches, cross bar etc.



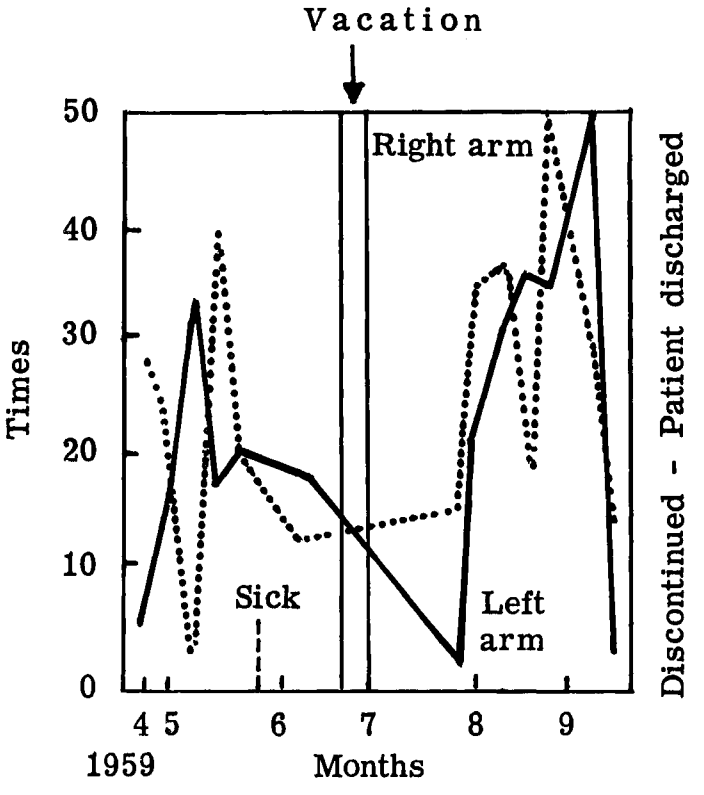
Walking	time — no limit, goal — 500 steps.	No. of independent steps taken without falling. Indicate type of apparatus.

Graphs being used for Occupational Therapy

Pre-Skills

Graph Titles	*Goal*	*Procedure*
Centering arm	time for 5 min. goal 20 times.	No. of times child can bring arm to centre of tray. Use any toy to motivate.
Elbow flexion-extension	time for 1 min. goal 20 times.	No. of times child can flex and extend. Range not important. Purpose to get shift in direction of motion.
Grasp-release	time for 1 min. goal 30 times.	No. of blocks (size dependent on child's hand) picked up from tray and released. Test only grasp. Move arm for him if necessary.
Pinch grasp	time for 1 min. goal 30 times.	No. of $\frac{1}{4}$ inch pegs child can grasp and remove from holes. Have him place wherever it is easiest.

REACH COMPARISON



J. T.
Rotary Athetoid
Drug - SOMA

No. of times he can reach toy on center tray - 10 minutes

Wrist flexion-extension	time for 1 min. goal 20 times.	No. of times child can flex and extend wrist. Use any toy to motivate.
Maintaining grasp	time for 5 min. goal 5 min.	Length of time child can hold object without dropping. Suggest spoon if sitting or cross bar if standing.
Two hand co-ordination	time for 1 min. goal 10 times.	No. of washers child can place on bolt. Hold bolt with sub-dom. hand, place bolt with dom. hand.
Relaxation	time for 5 min. goal 5 min.	No. of min. child can keep any part of body relaxed. Other parts may be stabilized. To test control of thrust or startle.

Head control	time for 5 min. goal 5 min.	Length of time child can balance 'Alexander ball' on head without head support.
Lip closure	time for 5 min. goal 5 min.	Length of time child can keep lips together.
Control of drooling.	time for 5 min. goal 5 min.	Length of time child can go without drooling first without activity, then incorporate into whatever he is doing.
Control of overflow	time — no limit goal 100%	Give child simple hand motion to perform 10 times. Graph % times he controls overflow.
Pre-feeding	time for 5 min. goal 30 times.	No. of times child can take hand from tray to touch mouth with lollipop or spoon.
Pre-typing	time for 5 min. goal 50 strokes	No. of random keys typed. May be used with finger, stick in hand or head typing.
Pre-writing	time for 5 min. goal 5 min.	Length of time child can keep arm in contact with paper on table.

Skills

Graph Titles	*Goal*	*Procedure*
Typing accuracy	time — no limit, goal — 90 — 100%	% correct letters while. . . . A. matching letters B. letters dictated C. copying words D. words dictated.
Typing speed	time for 5 min. goal 250 letters	No. of strokes typed in 5 min.
Feeding	time for 25 min. goal — 3 min.	Length of time to eat full dessert dish of apple sauce or pudding.
Undressing	time for 25 min. goal — or less for each article.	Length of time to remove any one article of clothing. Separate graph for each. A. shirt. B. pants. C. dress. D. shoes etc. Braces — anything applicable.
Dressing	time for 25 min. goal 5 min. or less for each article	Same as above.
Wheel chair propulsion	time for 1 min. goal — 20 yards.	Distance travelled on smooth floor in 1 minute.
Straw drinking	time for 5 min. goal 4 ounces.	No. of ounces child can drink in 5 min.

Graphs being used for Speech Therapy

Graph Title	*Goal*	*Procedure*
Breathing	20 Respiratory cycles per minute.	Average of 3 trials during quiet breathing.
Breathing	Controlled expiration for 20 seconds.	Blowing through 8″ plastic straw into glass of water.
Phonation	Voice level maintained at a lower level for 30 minutes.	Therapist counts number of times pitch level is too high. No cues given.
Phonation	A sustained phonation for 5 seconds.	Best sustained phonation in 3 attempts.
Phonation.	A sustained phonation for 10 seconds.	Best sustained phonation in 3 attempts.
Phonation.	Sustained phonation of (m-m) for 10 seconds.	Best of 3 trials. Good coordination of lip closure, phonation, and respiration are required.
Phonation.	10 'ma' syllables on a breath.	Best of 3 trials in a sitting position.
Phonation.	Voluntary 'ah' sustained for 10 seconds.	Best of 3 trials in a sitting position.
Articulation.	20 correct vowel productions in naming of pictures.	List of vowel sounds and stimulus words.
Articulation.	15 correct productions of (b) in imitation of words.	Stimulus words listed.
Articulation.	Production of (p) in 21 words.	7 words each are given in the medial, final, and initial portions of words. Words presented in random order.
Articulation	18 correct articulations without verbal stimulation.	Sounds being tested in the initial position of words: p, b, m, t, d, n, k, g, l. 2 trials per sound. Words picked at random.

Articulation.	10 correct imitations of 'yeah' and 'no.'	Each stimulus is to be given 5 times each in random order. The response must be isolated from babbling in order to be accepted.
Chewing.	Absense of tongue thrust — Better coordinated chewing pattern.	Graph for 5 minute period which includes placement of food and chewing. 'Thrust' means tongue seen outside lips.
Sucking.	3 ounces of liquid sucked in a 5 minute period.	Use 6ins. straw, small plastic bottle. Assist with lip closure.
Drooling.	No drooling during a 30 minute session.	Therapist counts number of drools occurring. No cues given to encourage better control.
Relaxation.	Control of bodily extensor thrust for 20 'yes' phonations.	20 questions answerable by 'yes' are asked. Control of extensor thrust of arms, trunk and head are required for successful performance.
Relaxation.	Maintain head control during speech attempts. 10 minutes.	Best time in 2 trials. Position of head: Flexed or upright, near midline not in line with shoulders.
Relaxation.	10 or more minutes without extensor thrust of the jaw.	Graph during quiet activity. Give no cues. Jaw opening of less then $\frac{1}{4}$ inch. approx.
Tension.	Maintenance of voluntary lip closure for 5 minutes.	Best of 3 trials.
Attention.	Maintain attention to a story for 10 minutes.	Listen while story is being read and/or relate story with appropriate comments to therapist.
Language Usage	Ability to tell therapist about Chapter 1 "Winnie	List stimulus pictures.

	the Pooh" by using at least one 3 word sentence for each of a series of 12 pictures.	
Language Usage	Consistent verbal yes-no response in 12 trials.	NG-yes, NG NG-no. Response must be isolated from babble. Random questions and materials used.
Language Usage	Accuracy in pointing to letters on a conversation board in a manner so that letters are clearly identified to the observer without aid of cues or context. 10 trials.	Write letters on a paper well in advance of graphing. Hold paper where only patient can see.

CHAPTER 6

The Use of Muscle Relaxants in Cerebral Palsy

P. HUME KENDALL

Reduction of the increased muscle tone that is associated with almost every form of cerebral palsy has invariably been one of the main objectives of those concerned with the practical management of the disease. Despite the present lack of knowledge of the intricacies of the neuro-psychological and neuro-muscular components of motor disabilities such as athetosis, spasticity, and rigidity, it seems reasonable to utilise any form of empirical therapy that results in a more normal muscular pattern. Methods which are successful in treating hypertonus in other chronic neurological diseases have been tried, particularly in the field of physical therapy, but the results have often been unspectacular.

Fountain and his colleagues (1960) showed that hot packs, ultrasonics and infra-red radiation effectively relieved muscle spasm for periods of ten to fifteen minutes after the treatment had finished, but the effect thereafter declined. A more successful response is observed following physical treatment; following carefully conceived and planned techniques, there is a temporary improvement in the clinical picture, but this only lasts for several hours at the longest and thereafter the patient relapses. Frequent repetition of therapy for prolonged periods is required to achieve even minor permanent improvement. Surgical techniques such as intrathecal phenol injections and stereotactic chemical ablation of the globus pallidus appear to have a marked action in permanantly reducing unwanted movement, but experience is limited and dangers great, although hemispherectomy has proved its value in reducing the incidence of fits (Carmichael 1961).

The administration of the newer groups of drugs which result in reduction of muscle tone presumably through an action on the central nervous system has brought about impressive changes in some cerebral palsied patients. A fundamental difficulty continues to be that of defining areas of involvement in cerebral palsy and, for the same reason, the precise level of drug activity is still in doubt. Although many investigators have been sceptical in the past over the value of chemotherapy in treating the motor disability of cerebral palsy, most will now agree that the preparations currently available will exert some effect in modifying the clinical pattern in athetoid, dystonic and spastic groups in cerebral palsy, even though the exact mechanism and extent is debatable.

Many factors complicate the treatment of the physical disability in cerebral palsy, such as perceptual disorders, speech and hearing defects, epileptic seizures and mental retardation. In addition to these, as a child develops, there is often a problem over what Keats *et al.* (1963) described as a 'non-psychological body anxiety,' as the

child tries to adjust himself to space and the problems of three-dimensional movements. In addition there is a 'psychological anxiety' that derives from a growing awareness of his plight. Both of these, if incorrectly treated, may lead to an undesirable mental attitude with a delay or reversal of progress. These appear in a most marked form during periods of rapid growth and are probably partly responsible for what Kendall and Bissell (1964) call the syndrome of adolescent deterioration. Apart from these central defects, there is the purely mechanical problem of overcoming the muscle weakness which is so frequently present in cerebral palsy. Sharrard (1961) has pointed out that the antagonist of spastic muscles are frequently extremely weak, a fact that is not always appreciated by those treating cerebral palsy; it is therefore essential that these groups should be developed, but the increased opposing muscle tone or unwanted movements frequently hinder this and have to be overcome before voluntary acts can be performed.

Whilst physical and educational therapy will almost always occupy the prime place in any programme, theoretically at least, drugs that can produce relaxation in the spastic muscle groups without disastrous side-effects will prove a useful form of therapy. In practice, however, claims for drugs of this type of activity have not always been borne out. Denhoff and Holden (1961) have demonstrated that many such preparations were either effective in doses intolerable to the children or else gave results that were almost identical to those of placebo. Schlesinger (1960) also reported that their main value in cerebral palsied patients was their ability to blunt the impact of the emotional environments, improved motor ability being only slightly associated with muscle relaxation. That is, both these authors consider that the activity of the drug on the skeletal system was largely, if not entirely, the result of its sedative or 'tranquillising' effect.

Assessment of Relaxants

Experience has shown that controlled studies are essential to assess the value of drugs in cerebral palsy. As Illingworth (1964) stated so clearly, clinical impressions in the assessment of a condition as variable as cerebral palsy 'just will not do.' Despite these comments, one will still find reports in the literature of trials which have been inadequately carrried out. It is therefore worth outlining the essential requirements of the controlled blind experiment. The active drug is compared with an inert substance in such a way that neither the patient nor those concerned with assessing the progress of the patient know which substance is currently being administered. As far as possible the circumstances are controlled so that other factors which might influence progress remain constant.

Difficulties also obviously arise over suitable parameters for evaluation. Unquestionably the newer drugs at present available exert an effect on many of the manifestations of cerebral palsy. In our own trials we demonstrated a definite increase in the passive range of movements of the knee and elbow joints with muscle relaxants, but the value of this and similar results is of uncertain value to the patient. It may be that selective local effect of this nature may be of assistance in attaining certain physical achievements, but this type of effect need not necessarily contribute to an overall improvement.

A sufficiently comprehensive picture is not obtained by studies of active and passive joint movements, muscle power and unwanted movements, nor do specific tests of ability in themselves yield sufficiently adequate information. A more fundamental approach is required to determine if the drug modifies primitive reflexes, improves perceptual disorders and diminishes the recognised educational 'blocks.' Future investigations must depend on this type of comprehensive approach, rather than upon a mere recording of clinical impressions and reports from therapists. It is essential moreover, that for any drug its immediate effects on the motor system, and its long term value as an aid to habilitation and education, should be assessed.

Review of the literature over the past ten years reveals reports on nineteen drugs claiming a value in reducing muscle power (Table I). Of these, mephenesin,

TABLE I

No.	Generic Name	Trade Names
1	Mephenesin	Myenesin, Mephate, Tolserol
2	Mephenesin Carbamate	Tolseram
3	Primidone	Mysoline
4	Methocarbamol	Robaxin
5	Meprobamate	Equanil, Miltown
6	Methaminobenzodioxan	Quiloflex
7	Carisoprodol	Soma, Carisoma, Rela
8	Hydrazino dyethyl triazine	"Ciba 13155"
9	Styramate	Sinaxar
10	Phenyramidol	Analexin, Trepidone
11	Zoxazolamine	Flexin
12	Chlorzoxazine	Paraflex
13	Tigloidine	Tiglyssine
14	Orphenadrine	Disipal, Norflex
15	Metaxalone	Skelaxin
16	Hydraxyphenomate	Listica
17	Emylcamate	Striatran
18	Chlordiazepoxide	Librium
19	Diazepam	Valium

primidone, meprobamate, methocarbamol, carisoprodol, chlordiazepoxide and diazepam have been the most widely used.

Mephenesin (Myanesin R, Mephate R)

This drug has the longest history of any of the muscle relaxants. In 1954 it was given intravenously to reduce spasm from trauma to joints, in cerebral palsy, in Parkinson's Disease and in spastic hemiplegia following cerebral thromboses. After a parenteral injection of 500 mgm., muscle spasm was reduced with preservation of voluntary power, although this was somewhat weakened. The effects of the drugs used in this way lasted for an hour to ninety minutes. Similar results followed the intravenous use of orphenadrine (Disipal R, Norflex R), or methocarbamal (Robaxin R). However, oral administration of all these drugs failed to reproduce these favourable effects and it is not clear why where is this lack of response. Blood levels of chlorzoxazone (Paraflex R) were reported as being elevated equally, whether the drug was given by mouth or by vein, yet only the parenteral route showed effective, objective reduction in muscle spasm.

The one controlled trail of mephenesin reported by Denhoff and Holden (1961) showed that the placebo was more effective in reducing spasticity and modifying unwanted movement than the active principle.

Primidone (Mysoline R)

Probably the first drug to find international general acceptance for treatment of cerebral palsy was primidone (Mysoline). This is a pyrimidine derivative related to phenobarbitone which is of value in the control of psychomotor epilepsy (see Chapter p. 52). Patients treated for epilepsy in the initial trials of the drug were noticed to show a concomitant improvement in their motor behaviour and it was thought that the drug may have an effect in altering muscle tone. Plum and Sparup (1958) reported 'favourable results' in 20 out of 30 cerebral palsied patients treated with a dose level of 2 to 10 mgm/kg. body weight. No result or a deterioration was noted in 13. These authors reported that the results were better in athetoid children than in spastic groups. Thorn (1962) compared the results obtained from treating cerebral palsied children with primidone and chlordiazepoxide and found favourable results in equal groups of cases, but stated that the individual patients reacted differently to both drugs. In the higher dose levels we have found that drowsiness is a troublesome feature and it is at this stage that relaxation was at a maximum. It is possible that the skeletal effect is a direct result of the sedative action.

Meprobamate (Equanil R, Miltown R)

This drug, which is a member of the carbamate group of 'tranquillo-sedatives', was shown to have a mild sedative and relaxant effect in animals. In an early clinical trial reported by Katz (1958), ten patients were treated with a dose of 200 mgm. daily, increasing fortnightly by 200 mgm. until a response was obtained. A weekly assessment was carried out of

(a) degree of muscle relaxation,
(b) magnitude of spasticity or involuntary movement,
(c) ease of handling,
(d) outlook and attitude,
(e) endurance,
(f) attention span,
(g) ability to learn.

This group was compared with nine patients not given meprobamate, but who were subjected to the same physical and educational programme. Those treated became more manageable, both physically and emotionally, during the eighty weeks of the study. They were less fatigued and more alert, whilst in 9 out of the 10 patients accelerated reading progress and ability to learn were observed. There was no direct effect on the attention span or learning ability nor was there any increase in quantitive reduction of spasticity or unwanted movement. On the other hand, Carter (1963) found a poor response to meprobamate in six brain-damaged patients with spasticity and subsequently a greater relief was obtained by the use of diazepam. Schlesinger (1960) considered that meprobamate was the first oral preparation to exert a true

pharmacological effect on the dystonic and athetoid groups, whilst it was little help to spastics; he believed its activity was largely the result of its sedative potentialities.

Carisoprodol

One of the most widely used of the growing group of drugs, and claimed to be of value in relieving spasticity as well as rigidity and athetosis, is N-isopropyl-2-methyl-2-propyl-1,3-propanediol dicarbamate, more commonly known as carisoprodol (Soma R, Rela R). This synthetically-produced substance is a very close chemical relation to meprobamate and is said to have muscle relaxant activity eight times the potency of mephenesin, without any interference with normal motor activity. The response is said to be rapidly prolonged but without appreciable side effects. Preliminary reports on clinical trials on this drug certainly appeared to be impressive. Phelps (1959) stated that his results indicated that carisoprodol is a safe and useful aid to therapy in patients with cerebral palsy and appeared to be superior to any other drug available for the relief of spasticity and rigidity. Spears (1960) concluded that there was increased relaxation in spastics and that extensor thrust and the tonic neck reflex were disrupted in certain patients. She felt that the drug helped to make the children more eager to walk and made activities of daily living more nearly normal. Grace Woods (1962) reported that 33 out of 46 cerebral palsied patients showed varying degrees of improvement although drowsiness and irritability proved to be a problem.

In disagreement with these findings were the careful and irreproachable trials conducted by Illingworth and others (1959) and Denhoff and Holden (1961). Illingworth *et al.* carried out a double blind trial in 47 children aged two to four years, treated as outpatients and objectively assessed at weekly intervals. There were no significant differences between the patients receiving the active principle and those on the placebo. It was concluded that under the conditions of the trial, carisoprodol exerted no beneficial effect on spasticity or athetoid movements. Denhoff and Holden (1961) studied the effect of mephenesin, chlorpromazine, reserpine, zoxazolamine, emylcamate and carisoprodol on spasticity. A standardised system of evaluation was developed and each drug was matched with a placebo. Particular studies of general behaviour were made as well as of neuro-muscular function. A favourable response of behaviour was observed ranging from 8 per cent with mephenesin to 53 per cent with zoxazolamine, and in neuro-muscular function from 9 per cent with reserpine to 56 per cent with mephenesin. When on placebo the behaviour rating improved from 17 per cent to 80 per cent and neuro-muscular function from 21 per cent to 50 per cent. The authors concluded that the 'placebo had a greater effectiveness in each of the two rated categories'. In a second report, Woods (1963), analysing the results of a double blind controlled trial, reversed her opinion on carisoprodol. She reported that there was no statistical proof that spastic patients on carisoprodol showed an overall greater improvement than those on placebo. In spite of the findings of her earlier trial there remained subjective evidence only that occasionally cases of spasticity improved on administration of the drug. Gooch (1963) in Melbourne came to the same conclusions after a double blind trial on seventeen children who were already subjected to a full programme of conventional therapy. Within the limitations of his trial, no evidence of any beneficial effect attributable to carisoprodol was obtained.

The conflicting evidence as to the value of this drug is difficult to interpret. There seems little doubt that carisoprodol may have a relaxant effect on skeletal muscles but the effects suggest that this does not appear to result from any specific local action on the muscles like curare, but by exerting a central effect, and it is interesting that those who claim to have had the best results report that drowsiness and irritability were common accompaniments. Nevertheless carisoprodol found wide acceptance and is still extensively used.

Chlordiazepoxide (Librium R)

This drug is the first member of a new chemical class of compounds, the benzodiazepins, which were shown by Randall *et al.* (1960) to have a unique effect in taming animals, and by Tobin and his colleagues (1960) to have a useful 'anti-anxiety' effect in human subjects. Other pharmacological effects first observed in animals and confirmed in humans include anticonvulsant, muscle relaxant, sedative and appetite stimulating effects, with ataxia at high doses. In addition to blocking chemical and electrical convulsions in mice, anticonvulsant effects were shown in monkeys in which chronic experimental epilepsy was produced by alumina cream applied to the cortex, or by pentylenetetrazol given intramuscularly. Certain minor pharmacological effects which were also minimal in both animals and human subjects include modifications of circulation, heart rate and other functions controlled by the autonomic nervous system. No adverse effect on the endocrine organs was found.

Chlordiazepoxide also has marked effects in modifying previously learned behaviour in rats and monkeys. In experiments in which rats or monkeys were conditioned to press levers to avoid electric shocks it shows effects in modifying the regularity and rate of response at doses one-tenth of those that cause depression of locomotor activity in rats or ataxia in monkeys. However, the taming effect in vicious monkeys is observed at doses much below those which interfere with the regularity of response in the conditioned avoidance experiments. In further experiments, the latency of learning by rats in a maze was decreased by chlordiazepoxide and the fixation of behaviour and compulsive rigidity in stress situations was abolished.

Chlordiazepoxide is metabolized almost completely in human subjects, with only small amounts appearing in the urine over several days. Part of the drug is metabolized and excreted in the urine and part is excreted into the intestine and passes out through the faeces. The half-life of a single dose or radioactive labelled drug is about one day in human subjects, but high blood levels from large oral doses are maintained for several days after stoping prolonged administration.

The clinical trials of the drug in cerebral palsy did not yield the dramatic effect that was expected, although in other disorders highly significant results have been observed. Thorn (1962) administered chlordiazepoxide in doses of 0·25 to 1 mgm/kg to 50 cases under reliable supervison for periods of one month to one year. The drug resulted in (a) reduction in spasticity, (b) improved performace of voluntary movements, (c) some reductions of hyperkinetic movements, (d) less disturbance of sleep by muscle activity and crying and (e) no definite effect on emotional reactions in spastics or athetoids.

The dose was increased at not less than five-day intervals until the desired effect was achieved. It was given either at night or divided into a small dose in the morning and a larger one at night to avoid sedation effects. The activity was usually noticable within a few days, often within 24 hours, independent of the aetiology, age, intellectual status and degree of handicap. The best results were obtained in athetoids and those suffering from rigidity; there was less benefit in spastics. Drowsiness was noticed in 20 out of 50 cases and irritability and depression in three out of six. Occasionally the children would not tolerate as little as 0·1 mgm/kg.

Keats and his colleagues (1962) administered the drug to 86 children in a maintenance dose of from 5 to 40 mgm. for an average period of 4·3 months. Forty-one children showed improvement in physical and emotional status without side effects, 35 showed no change, 10 deteriorated. He concluded that (a) the drug is tolerated better by spastic types of cerebral palsied than other groups, (b) athetotic and ataxic patients cannot tolerate it, (c) the drug improves the emotional status of the cerebral palsy children and aids progress in physical therapy schedules, (d) it exerts a muscle relaxant effect in the rigidity group, (e) it may improve involuntary movements in the athetoids, (f) it worsens gait and movement in the ataxic, (g) that a high percentage of the improvement obtained is in those in whom progress is hindered by anxiety and tension.

Bayliss and Gilbertson (1963) carried out a double blind cross-over trial in forty-one spastic children, demonstrating a significant difference between the effect of the placebo and chlordiazepoxide on the 'overall condition.' Improvement which occurred may have been partly due to a reduction in spasticity but was mainly due to improvement of sleep and behaviour. The patients' response was unpredictable and there was no significant difference between chlordiazepoxide and a placebo when they were assessed solely on their effect on motor disability. Emotional upsets and drowsiness were troublesome but no serious side effects were seen.

Debert (1964) using a technique which measured resistance of the spastic quadriceps muscle against positive extension, found that 'antispastic' action was present, but not marked in eight out of sixteen children. Holt (1964), on the other hand, in a controlled study on seven children found that the range of both active and passive dorsiflexion of the foot was increased more after doses of 20 to 30 mgm. daily than after a placebo. He pointed out that although the increased range of movement certainly occurred, this did not necessarily contribute to the total overall progress of the children which therefore had to be considered separately.

Diazepam (Valium R)

A second member of the benzodiazepin class which shows quantitatively similar effects is Diazepam (Valium). This drug was more potent than chlordiazepoxide in the initial trials in human subjects, and is at least equally well tolerated. In animal experiments it is five to ten times as potent as a muscle relaxant and has similar tranquillizing and anticonvulsant activity in mice. It is more potent in modifying the E.E.G. frequency in the cortical and limbic areas in the cat and in inducing sedation. It is less effective in reducing locomotor activity in rats, slightly less effective in reduc-

ing irritability in vicious rats with septal lesions and equally effective in modifying conditioned avoidance behaviour in rats. In monkeys, diazepam shows the same order of activity as chlordiazepoxide in calming vicious aggressive behaviour.

Theoretically, therefore, it should be more affective than chlordiazepoxide in controlling spasticity whilst having less central sedative effect. To some extent this has been confirmed by initial clinical trials. Phelps (1963) reported favourably on a group of nineteen in-patients suffering from cerebral palsy, treated with Diazepam. Sixteen of the patients were athetoid, two spastic quadriplegics and one an intermittent rigidity type. These patients possessed no physical skills and their handicaps made voluntary muscle control impossible or severely limited. Diazepam was given in a dose of 5 mgm. two or three times a day for periods of up to 13 months and regular evaluations of the drug effect were carried out by therapists, nursing and educational staff. Objective measurements of sitting, standing and jaw control and various other physical activities were charted over the period of treatment. The effect of Diazepam in reducing the physical handicap was considered to be fair to excellent in 70 per cent of the evaluations carried out, and in 50 per cent there was improvement in the emotional state. By far the best results were obtained in the athetoid and dystonic types. An unusual effect reported was that habitual grinding of the teeth and face scratching were limited in several patients. Phelps states that the general effect of the Diazepam was to make the children less tense and easier to manage. He considered that muscle relaxation, reduction of athetosis and increased voluntary control were independent of the improvement in motivation and emotional state.

Less dramatic claims are made by Keats and his colleagues (1963), who described a trial of the drug on 90 out-patients including spastic, rigid, athetoid, ataxic, atonic and mixed types . The dose level varied from 1 to 8 mgm. daily and therapy lasted for periods of up to 11 months. They claim that the results were 'good' in 19 of the out-patients, fair in 16 and poor in 32. Diazepam was very well tolerated in the athetoid children, most of whom responded well and were able to tolerate the large dose. It was not so well tolerated in the spastic, rigid and ataxic children. There was evidence that the results in the athetoid conditions could be enhanced by using parenteral dosage, but they would go no further than to say that results were 'encouraging.'

We have carried out double blind cross-over trials of Diazepam on a small number of patients at the Cerebral Palsy Assessment Centre at Guy's Hospital. All patients were treated with either Diazepam in a dose of 2mgm t.d.s. or a placebo tablet for a period of two weeks, and then switched over to the other tablet. Of ten adult hemiplegics, statistically significant improvement was observed in the range of passive movements in the knee and elbow joint. Tests of hand function and walking time showed that although a small majority improved on the active principle, statistically there was no significant improvement. In five cases of adolescent diplegia, there was again improvement in the passive movements at the knee joints, but walking times increased and tests of hand function were inconclusive. In five out of six athetoid cases there was a reduction in frequency of selected athetoid movements when on the active principle but there was also a similar reduction in three whilst on the placebo.

Out of a total of eighty-three cases receiving the treatment for 2,400 patients-days, the following side effects were observed:—

(a) *Severe, necessitating withdrawal:* Nausea and vomiting 5 per cent, vertigo 9 per cent, somnolence 10 per cent, ataxia 5 per cent, morbilliform rash 1 per cent.
(b) *Mild, not requiring withdrawal:* Lethargy 30 per cent, depression 15 per cent, hyperpyrexia 1 per cent.

Again it appeared that the athetoid patients tolerated high dose levels better than spastics and that the atonic group showed somnolence particularly severely. One patient who received two doses of 2 mgm. became unrousable for 36 hours.

Although trials of this drug are incomplete and further long term experience is essential, it seems likely that Diazepam exerts a measurable effect in modifying increased muscle tone in a reasonable proportion of cases. The remainder show no detachable response whatever. The drug is likely to prove of greatest value in either the dystonic group or in athetoids with tension, though it may be helpful in certain spastics. Dangerous side-effects have not been reported but drowsiness or depression may prove troublesome and necessitate withdrawal of the drug.

Further members of the benzodiazepins have been shown by Randall (1963) to have even greater potency as muscle relaxants, anticonvulsants and calming agents. Of these, the nitrodesoxylactam shows a very powerful relaxant and taming effect but is characterised by excitation in mice, rats, cats, monkeys and dogs at a low dose. This is such an unusual combination that the effects in human subjects and particularly in cerebral palsy will be watched with interest.

Indications for Administration of Muscle Relaxants

The reasons for giving this group of drugs in Cerebral Palsy are constantly changing but at present the following is a general guide:—

1. *Rigid and Dystonic Groups*

It is probably in this type of Cerebral Palsy that muscle relaxants have their greatest effect. Of these the benzodiazepin derivatives are the most useful. Initially Diazepam (Valium) 2 mgm. t.d.s. should be given but this can be increased quite rapidly up to a maximum of about 30 mgm. daily provided the child does not become drowsy. In fact lassitude and drowsiness are a useful guide to overdosage. The drug should be continued only whilst it is having a definite effect. In many cases the beneficial effect of the muscle relaxant appears to diminish after two or three months.

2. *Spasticity*

There is little to choose between Carisoprodol and Diazepam to produce a moderate reduction of spasticity in the limbs or trunk where it is desired to permit the achievement of certain specific objectives in the physical programme. Personally, we prefer Diazepam at the present time. In each patient the drug should be given in a dosage of 2 mgm. t.d.s. (or in the case of Carisoprodol up to 2 grams daily) for an initial period of ten to fourteen days, during which time careful assessment of the feature that it is hoped to modify should be carried out. If the desired effect is not achieved after this period the drug should be discontinued.

3. *Walking Difficulties*

Where walking is prevented by flexor spasticity of the muscles moving the hip or knee joint and it is felt that improvement might result in regaining walking. It should be noted that the walking speed may be slowed initially. The aim should be improvement in gait pattern and a period of intensive physical therapy should accompany drug administration.

4. *Psychological Effects.*

Where emotional problems are resulting in deterioration of the physical attainment and when anxiety and psychological tension are a marked feature, chlordiazepoxide (in a dose of 10 mgm. t.d.s.) appears to be the drug of choice, and in small doses may prove a valuable adjunct to physical and educational therapy.

5. *Athetoid Group.*

In a reasonable percentage of cases, reduction in the amplitude and frequency of unwanted movements may be achieved. It is impossible to forecast whether these effects will be prolonged or whether resistance to the drug will develop.

Contra-indications

It is our experience that deterioration in the patient's physical ability of the atonic and ataxic groups will almost inevitably follow drugs of the benzodiazepin group; somnolence, often severe, is a common complication.

So far no side effects which are a danger to the life or health of children or adults are reported to be associated with the muscle relaxants. Lethargy, depression and somnolence are frequently concomitant with required withdrawal but in the majority of cases these unwanted effects are mild and may even prove of value.

There is no place for administration of this or any other group of drugs to the cerebral palsied patient 'in the hope that it will do some good.' A relaxant drug should only be given with some specific objective in mind.

Several existing preparations described have definite effects in Cerebral Palsy which are of value in clinical practice. Better drugs will possibly be developed as the search continues for an ideal muscle relaxant. Such a drug should reduce or eliminate any involuntary activity and increased tone of specific groups of muscles without interfering with the normal voluntary use of such muscles, produce its effect within 30 to 40 minutes of its administration, and should result in no undesirable side effects. It should not require the use of other drugs or agents such as salicylates or sedatives to enhance its effect, and it should produce a clear effect in reasonable dosage. Finally, the effect should last for a reasonable time, say four to eight hours. Obviously such a preparation would be of immense value to those treating cerebral palsy, but as Schwab (1964) has pointed out, no such substance is known at the present time. However, the field remains promising and exciting and is of direct interest to all those concerned with cerebral palsy.

REFERENCES

Bayliss, S. G., Gilbertson, M. P. (1963) 'Controlled Trial of Chlordiazepoxide in Spastic Children.' *Dev. Med. Child Neurol.* **4,** 597.

Carmichael, E. A., (1961) 'Hemiplegia and hemispherectomy' *in* Hemiplegic Cerebral Palsy in Children and Adults. London: Heinemann/Spastics Soc.

Carter, C. H., (1963) 'Diazepam in the Management of Spasticity and Related Symptoms.' *Western Med.* **4.** Supp. 1. 34.

Debert, R. (1964) 'Librium' *Dev. Med. Child Neurol.* **4,** 445.

Denhoff, E., Holden, R. H. (1961) 'Relaxant Drugs in Cerebral Palsy' *New Engl. J. Med.* **264,** 475.

Fountain, F. P., Gersten, J. W., Sengir, O. (1960) 'Decrease in Muscle Spasm Produced by Ultrasound and Infra Red Radiation.' **41**.293

Gooch, J. M. (1963) "Carisoprodol in Cerebral Palsy: A Controlled Trial," *Dev. Med. Child Neurol.* **5,** 603.

Holt, K. S. (1964) 'Librium' *Dev. Med. Child Neurol.* **4,** 665.

Illingworth, R. S. (1964) 'Cerebral Palsy in Children and its Treatment.' *Dev. Med. Child Neurol.* **6,** 88.

——, Holt, K. S. (1959) 'A Double Blind Trial of Soma in Cerebral Palsy.' *Spastics Quart.* **9,** 34.

Katz, B. E. (1958) 'Education of Cerebral Palsied Children. The Role of Meprobamate; a Preliminary Evaluation.' *J. Pediat.* **53,** 467.

Keats, S., Kambin, K., Nordlund, T. (1962) 'Clinical Experience with Chlordiazepoxide (Librium) in Infantile Cerebral Palsy.' *Dev. Med. Child Neurol.* **4,** 336.

——, Morgese, A., Nordland, T. (1963) 'Role of Diazepam in the Comprehensive Treatment of Cerebral Palsied Children.' *Western Med.* **4.** Supp. 1, 22.

Kendall, P. H., Bissell, E. M. (1964) 'Deterioration of the Cerebral Palsied at Adolescence.' *Dev. Med. Child. Neurol.* **6.** 80.

Phelps, W. M. (1959) 'Preliminary Institutional Evaluation of a New Drug in Cerebral Palsy: N-isopropyl-2-methyl-2 propyl-3-propanediol dicarbamate (Soma).' *Arch. Pediat.* **72,** 243.

—— (1963) 'Observations of a New Drug in Cerebral Palsy Athetoids' *Western Med.***4** , Supp. 1, 5.

Plum, P., Sparup, K. (1958) 'Mysoline and Meprobamate in Cerebral Palsy.' *Acta Paediat.* **47,** 260.

Randall, L. O. (1963) 'Psychosomatic Medicine.' Ed. J. H. Nodine & J. H. Moyer. Lea and Febiger, New York. p. 475.

——, Schallek, W., Heise, G. A., Keith, E. F., Bagdon, R. E. (1960) 'The Psychosedative Properties of Methaminodiazepoxide.' *J. Pharmacol. exptl. Ther.* **129,** 163.

Schlesinger, E. B. (1960) 'The Rationale of Treatment of Motor Disorders with Muscle Relaxants.' *Ann. N.Y. Acad. Sci.* **86,** 238.

Schwab, R. S. (1964) 'Muscle Relaxants.' *Practitioner,* **192,** 104.

Sharrard, W. J. (1961) 'The Mechanism of Deformity in Cerebral Palsy.' *Proc. roy. Soc. Med.* **54.** 1016.

Spears, L. E. (1960) 'Clinical Evaluation of Carisoprodol in Handicapped Children.' *Ann. N.Y. Acad. Sci.*, **86,** 242.

Thorn, I. (1962) 'Primidone and Chlordiazepoxide in Cerebral Palsy' Dev. Med. Child Neurol. **4,** 325.

Tobin, J. M., Bird, I., Boyle, D. E. (1960) 'Preliminary Evaluation of Librium in the treatment of Anxiety Reactions.' *Dis. nerv. System.* **21,** 11.

Woods, G. (1962) 'Preliminary Trial of Carisoprodol in Infantile Cerebral Palsy.' *Dev. Med. Child Neurol.* **4.** 28.

——, (1963) 'Double Blind Trial of Carisoprodol,' *Dev. Med. Child Neurol.* **4,** 499.

CHAPTER 7

Anti-convulsant Drugs

ERIC DENHOFF

The majority of cerebral palsied children (but more spastics than athetoids) have either clinical seizures or abnormal electro-encephalograms. As uncontrolled seizures can lead to further damage, the treatment of seizures should take precedence over any other type of treatment. The control of seizures may be easy or difficult to achieve depending on the type and the severity of seizures and the child's response to drug treatment. Drugs cannot 'cure' a susceptibility to seizures, but they can raise the seizures threshold so that in most cases seizures are prevented or, at worst, occur rarely. As with all drug therapy, drugs of known low toxicity are tried first and changes to newer medications that are less predictable are made only if seizures are uncontrolled (Scholl 1963). Combinations of drugs are frequently needed to keep the incidence of seizures to a minimum. Several months may be needed to reach a relatively seizure-free state, and the child should continue therapy for at least two or three years after the last seizure. Then medication should be slowly diminished and finally discontinued if the child remains free of convulsions. On such a regime the child can live as full and normal a life as his other capacities will allow.

Epilepsy occurs in all its varied forms in cerebral palsy. It is defined (McHenry and Levens 1963) as 'a symptom complex which is characterised by recurrent transient episodes in which there is usually an alteration in the state of consciousness, as a rule associated with convulsive movements and/or disturbances in feelings or behaviour'. Levens's modification of Carter's (1961) classification of seizures is shown in Table I.

Particularly in cerebral palsy the symptoms and signs of epilepsy are difficult to differentiate from complaints of emotional origin. Behavioural mannerism may represent seizure activity and where there is a poor response to other treatment *a diagnostic trial of an anti-convulsant is permissible even without any E.E.G. evidence of seizure activity.* Recurrent headache and stomach-ache are symptoms which we have treated successfully in this way. Another little-recognised phenomenon is that the startled behaviour in infants may have a similar origin, and cautious administration of anticonvulsants may make feeding, which has been very difficult, easier and lead to an improvement in the general condition of the child.

The Drugs

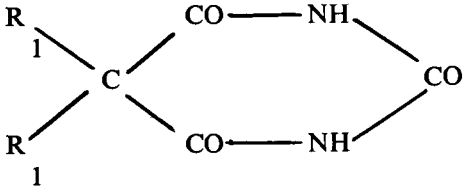
Six major groups of drugs are currently used in the management of convulsions. These are the barbiturates, hydantoinates, oxazolidines, acetylurias, pyrimidines and succinimides (Flack and Regan 1960).

TABLE I. Classification of Seizures

1	*Simple Febrile Convulsions*
2	*Minor Motor Seizures* (a) Infantile spasms (b) Akinetic seizures (c) Myoclonic jerks
3	*Abdominal Type*
4	*Petit Mal*
5	*Grand Mal* (a) Generalised onset (b) Focal onset
6	*Psychomotor*
7	*Focal* (a) Local, *e.g.*, aphasic (b) Jacksonian (i.) Motor (ii.) Sensory
8	*Rare Types* (a) Myoclonic variants (b) Sensory (i.) Induced (ii.) Receptive
9	*Combined Types*

Barbiturates

Barbiturates have dominated the treatment of seizures for the past half century. They are not now the drug of first choice and are giving way to Primidone (Mysoline R) but they are still very widely used. Despite this long history we still lack adequate controlled trials of their value. Barbiturates are based on the general formula:



Toxic effects: In general these are uncommon, although skin reactions and drowsiness occur. The drugs are also said to aggravate petit mal seizures on occasion. But, paradoxically, in cerebral palsy these drugs have a bad effect on the hyperkinetic behaviour disorder. They increase the hyperactivity and for this reason are of rather limited value in cerebral palsy.

Phenobarbital (*Luminal* R) is the most widely used and has the best anticonvulsant action. It is also a sedative. It is effective in the control of both major and minor motor seizures. The effect of a single dose lasts 6-12 hours and there is very little accumulative effect. For adequate effect the drug must be repeated every eight hours.

It is more effective on an empty stomach but the action lasts longer when taken after meals. It may be given as a tablet or as an elixir. In the parenteral form, Sodium Phenobarbital is effective in controlling status epilepticus or for immediate control of a seizure. The usual dose under these circumstances is ½ gr. (30 mg.) to gr. 1½ (100 mg.) intramuscularly. It can be repeated in twenty minutes if the seizure is not controlled.

TABLE II (PHENOBARBITAL)

Age	Starting Dose	Average Dose	Maximum Dose
Infancy	8 mg. (grl/8)	16 mg. (gr¼) t.i.d.	32m g. (½gr) t.i.d.
Children	16 mg. (gr.¼)	32 mg. (½gr) t.i.d.	65 mg. (1gr) t.i.d.
Adolescents, Adults	gr.¼	32 mg. (½gr) t.i.d.	100 mg. (1½gr) t.i.d.

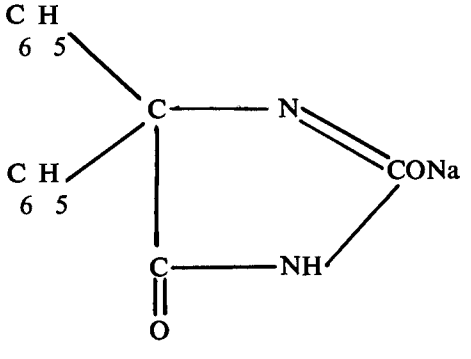
Metharbital (Gemonil R) is a synthetic barbituric acid derivative which has less of a sedative action than phenobarbital. It is especially effective in the control of myoclonic seizures and in conditions where seizures are the reflection of organic brain damage; it is therefore particularly useful in cerebral palsy, especially when used conjointly with other anticonvulsant agents in the control of petit mal epilepsy, minor motor epilepsy, or infantile spasms (Perlstein 1950).

In infants and other young children the starting dosage is 50 mg. once or twice daily, which may be gradually increased to 100 mg. three times a day. Higher doses are not usually warranted. There are few toxic reactions to this drug, although skin rash and transient drowsiness are reported.

Methylphenobarbital (Mebaral R) is a drug with a very similar action to phenobarbital, although the dose required is twice as large. It is used primarily when a child is hyper-sensitive to phenobarbital, although this is rare. More often it may be used when one does not wish the parent to know that a 'common sleeping pill' has been prescribed.

Hydantoins

Phenytoin (Dilantin R and Epanutin R). This is by far the most widely used hydantoinate. It is the sodium salt of 5.5-diphenylhydantoin and it has the following structural formula:



It is a highly effective anticonvulsant. Livingston (1956) who has reviewed his experience with this drug, feels it is the least hypnotic and the most effective of all the anticonvulsants. It is most useful in the control of generalised and psychomotor seizures. It is available in liquid suspension or tablet form and also for parenteral use.

It is an excellent drug for controlling cerebral seizures (major motor, grand mal seizures) and it is also very effective in controlling psychomotor (temporal lobe) seizures and diencephalic, autonomic, thalamic, or hypothalamic seizures. These forms of epilepsy may be manifested as recurrent attacks of dizziness, abdominal pain, headaches, cyclic vomiting, emotional instability, fainting spells, loss of consciousness, and other vegetative disturbances.

Toxic Effects. Untoward reactions most commonly occurring in the central nervous system are disturbances of equilibrium (ataxia or unsteadiness of gait) and diplopia. Ataxia will disappear within one or two weeks after the drug dosage has been reduced but may occasionally persist as long as six months. Ataxia may develop after the child has tolerated Dilantin for a long time. This has been particularly noticeable with the suspension form of the drug and may have been due to an overdosage due to problems of drug particle distribution within the suspension. Nystagmus, dysarthria and drowsiness are also common complications but again may reflect overdosage. Tremors, dizziness, and a sensation of walking on air have been reported, as also have headaches, and belligerent and destructive behaviour in children.

Skin rashes, which frequently appear as a measles-like eruption, are not uncommon. The rash usually appears ten to fourteen days after the initial dose of Dilantin and is frequently associated with fever and lymphadenitis. If the rash involves the throat and buccal mucosa, a differential diagnosis between drug sensitivity and measles is difficult. Other eruptions which have been reported are scarlatiniform and urticarial eruptions, but purpuric rashes and exfoliative dermatitis are rare, although they occasionally occur, particularly if the preparation is given in combination with other anticonvulsants.

Hyperplasia of the gums is a not uncommon complication and represents an individual sensitivity to the drug. It is not related to drug dosage. In most cases the hypertrophy will regress to normal within a year after withdrawal of the drug. It is it not usually necessary to withdraw the drug unless the hyperplasia is so marked that it interferes with chewing or is disfiguring. Diphenhydramine (Benadryl R) has been reported to be of some value in reducing gum hyperplasia but proper dental hygiene is a surer form of prophylaxis. Dilantin sometimes increases the frequency of petit mal attacks and if possible should not be used when petit mal is suspected.

Hypertrichosis, which often occurs predominantly on the extensor surfaces of the extremities, but also on the face and trunk, is a common complication when the drug is used over a long period. It usually disappears within a year of withdrawal of the drug. Other complications are gastrointestinal upsets — constipation, anorexia and abdominal pain, but these are rare, as are albuminuria and hematoporphyrinuria. Agranulocytosis, megaloblastic anemia and leukemoid reactions have also been reported on rare occasions. Other rare complications are myocardial damage and a change in the cardiac rate. A few cases of chronic fibrosis of the lungs have also been

considered a complication arising from the use of Dilantin (Bray 1959)).
Dosage: Livingston (1956) outlines the following average, starting and maximal dosage for Dilantin.

TABLE III (DILANTIN)

Age in Years	*Starting Dose*	*Maximal Dose*
Under six	32 mg. (gr. ½) thrice daily	100 mg. (gr. 1½) t.i.d.
Six-fourteen	100 mg. (gr. 1½) twice daily	200 mg. (gr. 3) t.i.d.
Over fourteen	100 mg. (gr. 1½) thrice daily	200 mg. (gr. 3) q.i.d.

Because of the cumulative effect of Dilantin, the drug can often be given as a single nightly dose. But as the dosage varies considerably from patient to patient it is wise to initiate the drug in small divided doses and gradually add increments until the maximum tolerated level has been reached. Unfortunately, it is not unusual to find that a dose which will control seizures will also produce ataxia and/or diplopia.

Ethotoin (Nirvard R) is a hydantoinate which may be effectively combined with Mysoline to control mixed types of seizures. Toxic effects are comparable to Dilantin.

Mephenytoin (Phenantoin R and Mesantoin R) is another member of this group which has a greater sedative action than Dilantin. Unfortunately the incidence of toxic reactions is higher and these take the form of an unpredictable incidence of haematological complications such as anaemia, agranulocytosis and leukemoid reactions. Periodic blood counts are required over a long period. Drowsiness and skin eruptions, morbilliform in type, also occur. It is usual to start with a dose of 50 mg. once a day for a week, and slowly add increments of 50 mg. until an effective drug level is reached; usually this is 100 mg. 3-4 times a day in children.

Oxazolidines

The most widely used of these drugs is *Trimethadione* (Tridione R) which is about 80 per cent effective but, unfortunately, is also potentially highly toxic. It is of specific value in one or all components of petit mal epilepsy, although it tends to aggravate the grand mal reactions.

Toxic Effects: These may be mild or severe. The mild signs or symptoms include dizziness, ataxia, vertigo, lack of concentration, nervousness, insomnia, confusion, stupor, hallucinatory psychosis, disorientation, memory defects, diplopia, blurring of vision, paracentral scotoma, pain in the eyeball, difficulty in focusing the eyes, dilated pupils, temporary papilloedema, decreased day vision, macropsia, photophobia (29·4 per cent), skin rashes (9 per cent), irritability, restlessness and difficulty in controlling behaviour (8·1 per cent), nausea and epigastric distress (6·7 per cent), fatigue (6·7 per cent), sleepiness and drowsiness (4·7 per cent), hiccough (1·2 per cent), sneezing, headaches, transient sore throat, nosebleed, poor circulation, muscle pains in the extremities, muscle instability, anorexia, transient albuminuria and generalized swelling of the joints with pain and fever.

Photophobia is the most common of this very large range of side effects and occurs

more often in adolescents and adults than in children. It clears up spontaneously even if medication is continued. Skin eruptions, in the form of morbilliform eruptions, urticarial, acneiform and macular eruptions resembling angioneurotic edema are also quite common.

The more serious toxic reactions include severe hematological, cutaneous and renal changes. The hematological effects range from mild reduction of neutrophils to a serious cytopenia with pancytopenic changes in both the peripheral blood and the bone marrow. Nephrosis is the most common renal complication, but albuminuria alone is not uncommon. Fortunately, pyelonephritis does not often occur. Serious cutaneous reactions range from urticaria and angioneurotic edema to a full blown Steven-Johnson's Syndrome. Exfoliative dermatitis with stomatitis is also a not unusual complication.

In infants and young children the initial dose should be 100 mg. three times a day, while in older children 200 mg. three times a day going up to 300 mg. in adolescents and adults is prescribed. A maximum dose of 2 g. daily is advised in adults, although higher doses are used.

Paramethadione (Paradione R) is a homologue of Tridione and is used in a similar manner and has the same dosage. Its side effects appear to be fewer and less severe than with Tridione, but similar complications do occur.

Acetylureas

Phenacemide (Phenurone R) is the best of the anticonvulsant drugs for mixed types of seizure, but it is also the most toxic. When seizures cannot be controlled with a variety of anti-convulsant combinations, control can be often achieved with Phenurone alone or in combination with other anticonvulsants.

The average child's dose is 500 mg. three times a day, although slightly larger doses can be given. Extreme caution must be taken to prevent liver damage and blood dyscrasias. The precautions for preventing toxic drug reactions must be adhered to rigidly with this drug.

Pyrimidines

Primidone (Mysoline R) has become the drug of first choice in the treatment of generalized seizures and psychomotor attacks (Livingston 1954), and is preferable to diphenylhdantoin because, to date, its long term toxic effects are fewer.

Toxic Effects: When treatment starts, one expects an immediate drowsy effect which is sometimes associated with headaches and which may last for three or four days. For this reason an initial dose of 50 mg. at bedtime is prescribed. Side effects are usually minor but those which have been reported include nausea, anorexia, vomiting, fatigue, hyper-irritability, diplopia and nystagmus. A morbilliform eruption is sometimes seen, but disappears with reduction or withdrawal of the drug. As with other anticonvulsants, megaloblastic anaemia, agranulocytosis and leukemoid reactions are sometimes reported; 15mg. of folic acid daily will help correct these deficiencies and allow primidone therapy to continue. A common cause of drowsiness with this drug is overdosage with the suspension. The recommended dosage for this drug is outlined in Table IV.

TABLE V Drugs commonly used in Convulsive Disorders

Drug	*Dosage*		*Type of Seizure*					*Side Effects*
	Under 6 yr.	Over 6yr. and adults	Petit Mal	Grand Mal	Psycho-motor	Focal	Minor Motor	
BARBITURATES								
Phenobarbital	15 to 32 mg. t.i.d. between 3 and 6 yr. 32 to 64 mg. t.i.d.	64 to 100 mg. t.i.d.	+	+++	++	+		Drowsiness, dizziness, ataxia, nystagmus, visual blurring, skin rash. Irritability particularly in cerebral palsy.
Methylphenobarbitone	Twice or three times those of phenobarbitone		+	+++		+		Same as phenobarbitone
Mephobarbital 'Prominal' (R)								
Metharbital Methylbarbitone 'Gemonil' (R)	50 to 100 mg. t.i.d.			++		+		Same as phenobarbitone
HYDANTOINS								
Phenytoin Sodium Diphenylhydantoin Sodium 'Dilantin' (R) 'Epanutin' (R)	32 to 100 mg. t.i.d.	100 to 200 mg. t.i.d.		+++	++	+	+	Drowsiness, dizziness, headache, insomnia, restlessness, diplopia, ataxia, vertigo, nystagmus, slurred speech, skin rashes, epigastric distress, nausea, gum hypertrophy, megaloblastic anaemia, lymphadenopathy, hirsutism, abnormal EEG.
*Methylphenythylhydantoin 'Mebroin' (R) 'Mesantoin' (R)	50 to 200 mg. t.i.d.	100 to 300 mg. t.i.d.		++	+	+		Skin rashes, purpura with decreased platelets, leukopenia, bone marrow depression, lymphadenopathy, hepatitis, periarteritis, nodosa.
OXAZOLIDINES								
Troxidone Trimethadione 'Tridione' (R)	150 mg. b.i.d. to 300 mg. t.i.d.	300 mg. b.i.d. to 600 mg. t.i.d.	++		+		+	Photophobia, drowsiness, nausea, diplopia, vertigo, irritability, headaches, bone-marrow depression with anaemia, leukopenia, nephrotic syndrome.

ACETYLUREAS Phenacemide 'Phenurone' (R)	250 to 1000 mg. t.i.d.	500 to 2000 mg. t.i.d.		+	++		+	Psychiatric disturbances, depression, acute psychoses, irritability, headache, drowsiness, dizziness, blood dyscrasias, nephritis, skin rashes, anorexia, nausea.
PYRIMIDINES Primidone 'Mysoline' (R)	62.5 mg. b.i.d. to 125 mg. q.i.d.	250 mg. b.i.d. to 500 mg. q.i.d.		+++	++		+	Drowsiness, dizziness, ataxia, slurred speech, nystagmus, impotence, nausea, vomiting, epigastric distress, leukopenia, anaemia.
SUCCINIMIDES Ethosuximide 'Zarontin' (R)	250 mg. daily	250 mg. b.i.d. increased by 250 mg. wekly to maximum of 200 mg. b.i.d.	+++					Drowsiness, dizziness, nausea, but no serious side effects yet reported.
Phensumixide 'Milantoin' (R)	250 mg. b.i.d. to 500 mg. t.i.d.	500 mg. b.i.d. to 1000 mg. q.i.d.	++				+	Drowsiness, ataxia, irritability, headache, nausea, vomiting, skin rashes, microscopic haematuria.
Methsuximide 'Celentin' (R)	150 mg. to a maximum of 2400 mg. (average 300 mg. t.i.d. or q.i.d.) No definite dose established for children		++		+			Drowsiness, irritability, ataxia, blurred vision, diplopia, anorexia, vomiting, diarrhoea, constipation, skin rashes, leukopenia, periorbital hyperaemia.
BROMIDES Sodium, Potassium or Ammonium bromide	Start with a dose of 30 mg. t.i.d. Increase by up to 300 mg. weekly.			++				Drowsiness, mental confusion, skin rashes.

*Many of these drugs are made up in combination (for example 'Mebrin' contains Mephobarbital and diphenylhydantoin), but such examples are not included in this list.

TABLE IV (MYSOLINE)

Week	Day	Children under 8 yrs.	Children over 8 yrs.
First	1—2	50 mg. daily	125 mg. daily
First	3—5	100 mg. daily	
First	5—7	150 mg. daily	
Second		200 mg. daily	250 mg. daily
Third		250 mg. daily	250 mg. twice daily

Succinimides

Ethosuximide (Zarontin R and Ethosuccinimide R) is a useful drug in treating petit mal epilepsy and appears to be the drug of choice in the treatment of this condition because of the relatively small incidence of toxic side effects. Reports of agranulocytosis have, however, been issued recently. Other toxic reactions described are nausea, gastric distress, drowsiness, dizziness and headaches. Skin rashes, and temporary increases and changes in appearance of the mononuclear leukocytes, have also been reported. An odd case of aplastic anaemia has been reported, when the drug was given in combination with other anticonvulsants, as well as a case of transient albuminuria.

The dosage for young children is 0.25 gm (250 mg.) a day, and for older children 0.25 g. (250 mg.) twice a day. It may be necessary to increase the dose to a higher level as 1.5 g. in divided doses in order to achieve effective seizure control.

Phensuximide (Milontin R). This drug is also used in petit mal epilepsy, and while it is not so effective as Ethosuximide it is attractive, because it can also control generalized seizures. The toxic side effects are similar to those of Ethosuximide, although not so common. The dosage is usually 0.5 g. three times a day. It is available as a suspension which is frequently taken easily by young children. If it is not effective within two weeks, it should be discontinued.

Amino-glutethimide (Elipten R), an analogue of Doriden, is a widely used non-barbiturate sedative which has anticonvulsant action for generalised forms of epilepsy. It is also recommended for other forms of epilepsy but experience of its use is limited. It is available in tablets of 125 mg. and 250 mg. It can make a child very sleepy. A generalised morbilliform eruption is an early complication.

Table V, based on McHenry and Levens (1963), summarizes the drugs used in the treatment of epilepsy. Scholl (1963) has recently outlined the most commonly used anticonvulsant drugs. This paper briefly reviews the current status of seizure control and points out that often such diverse drugs as Quinacrine (Atabrine R), Amphetamine, Desoxyn, Acetazolamide or Diamox may be needed as adjunctives before effective control can be achieved. Bromides and ketogenic diets are now rarely used but may be needed on occasion. It is worth while to remember that in certain cases of amino-aciduria (phenylketonuria is an outstanding example) change of diet or elimination of an offending dietary agent may help control seizures. The author recently eliminated cow's milk from the diets of certain cerebral palsied children with seizures. They all had suggestive amino acid abnormalities in the urine and seizure control in these difficult cases seemed easier after this dietary restriction.

REFERENCES

Bray, P. F. (1959) 'Diphenylhydantoin (Dilantin R) after 20 years'. *Pediatrics*, **23,** 151-161.

Carter, S. (1961) Lectures: 'Significance of Seizures,' and 'Medical Therapy of Seizures.' Postgrad. course in pediatric neurology. Columbia University, New York., May 1961.

Flack, F. F., Regan, P. (1960) Chemotherapy in Emotional Disorders. New York; McGraw-Hill.

Livingston, S. (1954) The Diagnosis and Treatment of Convulsive Disorders in Children. Springfield, Illinois: Thomas.

——, (1956) 'Treatment of epilepsy with Diphenylhydantoin Sodium (Dilantin Sodium).' *Postgrad. Med.*, **20,** 584-590.

McHenry, Jr. L. C., Levens, A. J. (1963) 'The treatment of epilepsy with drugs.' *Dev. Med. Child. Neurol.* **5,** 167.

Perlstein, M. A. (1950) 'Gemonal (5.5 diethyl l-methyl barbituric acid), new drug for convulsive and related disorders.' *Pediatrics*, **5,** 448-451.

Scholl, M. D. (1963) 'Treatment of seizure disorders (epilepsy).' *N.E. Med.J.*, **269,** 1304.

CHAPTER 8

Drugs, Behaviour and the Family

ERIC DENHOFF

Behavioural Disorders in Cerebral Palsy

The use of drugs which can favourably alter behaviour in cerebral palsy demands an understanding of the relationship of the organic and emotional components which contribute to such behaviour problems. It is our feeling that the hyperkinetic impulse disorders reflecting dysfunction of the diencephalon (thalamus and hypothalamus) underlie the majority of behaviour adjustment difficulties in cerebral palsy. Emotional problems arise from primary disability of hyperkinesis, and develop into a host of secondary problems as the child develops in his family environment (Denhoff and Robinault 1960, Laufer and Denhoff 1957). There will, of course, be instances where emotional problems exist alone or over-ride the basic organic disorder and here drugs will serve as adjuncts to psychotherapy.

Typically, hyperkinetic disorder starts with a fretful or querulous infant who is tense or rigid, and unable to respond to, or resists 'mothering.' The mother feels inadequate and complains to the physician who may counsel her or prescribe phenobarbital or another barbiturate for the child. These drugs often seem to agitate the child more, because of the paradoxical effect of barbiturates on a brain-damaged child. The child may become more irritable, unmanageable and active. Soon the mother develops further feelings of inadequacy and even hostility towards the child, when medical attempts fail to modify behaviour. Within the first year an entire family is engulfed in hostility towards a child who by this time is not only hyperactive and behaves explosively, but is irritable and agitated. The child is unable to control his behaviour because of the diencephalic dysfunction. He now senses the hostility of those around him. As he grows older he 'acts out' by resisting the family through a variety of hostile anti-social activities. On the other hand, his personality may be such that he withdraws into a shell and becomes anxious, tense or withdrawn. Here drugs may help the child accept therapy, or make him more amenable to it. Drugs are not replacements for psychological guidance. But parents often comment that they make the child 'liveable with' while other therapeutic measures are being devised. Fortunately the syndrome tends to clear up spontaneously as the child grows older; the particular time at which this will occur in individual cases is unpredictable. It is usual to withdraw drug therapy once a year (during the summer holidays) and see if the syndrome is still present. If it is, treatment continues for another year.

Where the hyperkinetic impulse disorder is not present a decision must be made about the emotional attitudes of the child. Fear and body anxiety are not uncommon in cerebral palsy and in these cases a tranquilizer is indicated. Often this will reduce anxiety and lessen tension, and as a result improvement will follow. Recent advances have made it possible to develop drugs which reduce skeletal muscle hypertonia as

well as favourably altering anxiety. (see p. 43). The physician prescribing such a drug will often be impressed by the change he sees in the child and his parents during the following visits. However, he must remember the 'placebo' effects of patient-family-physician interaction. Thus, if he substitutes placebo, very often progress will continue in the same positive direction. On the basis of such experiences, a placebo can often become the initial drug given. However, in a proportion of cases, the physician will be convinced that the drug is more effective than the placebo. The physician may reasonably use drugs not only for their effect on the child, but to help him gain psychological rapport with the parents. The initiation of drug therapy may make the parents feel that 'something is at last being done for their child.'

Drugs thus seem to provide an early impetus for progress and should be used as a major resource in the early treatment of cerebral palsy. They alter behaviour and can help improve body movement if properly prescribed, and the parents, who may have seen no change in these items since cerebral palsy was first suspected, start to become hopeful that help for their child is possible. At this stage, it must be emphasized to the parents that drugs alone are inadequate and have been used to make various types of therapy and guidance possible. When a child can accept 'therapy' and group participation, drugs are discontinued. The parents are told that progress has been such that the child no longer needs such a 'crutch'. Other behavioural disturbances which the cerebral palsied shares with the normal child, such as difficulty in going to sleep or in feeding, may respond to drugs.

Diagnosis

The diagnosis of these behavioural disorders is often not very difficult. The child's behaviour in the clinic alone may give good grounds for a diagnosis of hyperkinetic impulse disorder. A careful history taken from the parent, together with the collection of information from those (teachers and therapists) who have the opportunity to observe the child for longer periods than the physician are essential features of diagnosis. In doubtful cases we have found the photometrazol test a useful tool.

This EEG technique (first described by Gastaut 1950) has provided a clinical method for exploring certain subcortical structures, especially the diencephalon and the thalamus, and has been adopted for use with children. It consists of administering metrazol intravenously in a standardised way while simultaneously stimulating the patient by flashes of light from a powerful stroboscope at a set frequency. The end point is indicated by the appearance of a specific discharge in the EEG. It is recorded as the photometrazol threshold, or the amount of metrazol in milligrams per kilogram of body weight, required to evoke this specific response. A low threshold is thought to evoke such a specific response. In studies of children between seven and twelve years of age (Laufer *et al.* 1954), the following range of photometrazol threshold was found in milligrams of metrazol per kilogram of body weight.

Normal	6.5 and above
Borderline abnormal	5.1 — 6.4
Abnormal	Less than 5

Such findings are scientifically interesting; they became clinically important when it was found that children with organically derived behavioural dysfunction (on the basis of history and physical findings) have a low photometrazol threshold (in the region of 5.1 or less). Following oral administration of the racemic or dextro-amphetamine, the photometrazol level returns to normal within a week, while behaviour concomitantly improves. (The action of this drug is further discussed by Marrazzi, p. 16).

Even without the sophistication of this test, a week or two's trial of the specific drug will often seem to confirm the diagnosis of the disorder, so that the pharmacological approach to behaviour problems is at first diagnostic and then becomes therapeutic. Drugs which can be used both to differentiate an underlying organic component from environmental behaviour components and to treat the disorders are:

(1) Amphetamine and related derivatives for the hyperkinetic impu]se disorders;

(2) Phenothiazine and related derivatives for fear and anxiety.

Drugs which influence psychological and mental processes and modify human emotions and behaviour are known as psychotropic agents (Doyle 1962). They usually act specifically in an inhibitive manner on the thalamus and hypothalamus (diencephalon), causing stimulation or depression, or directly act on the whole central nervous system. The barbiturates, which are psychotropic, are contra-indicated in cerebral palsy since they often have a paradoxical excitatory effect when the diencephalon has been impaired. The clinical importance of this will be expanded when the use of amphetamine is discussed.

There are other substances besides drugs which may influence behaviour in cerebral palsy. These include vitamins, hormones and amino acids. For convenience they are grouped together here although the symptoms in some instances are not behavioural. Such rarely mentioned members of the armentarium are discussed to emphasize that there is much to be learnt about their role in cerebral metabolism. When their role is clarified other pharmacological agents may become available which will be useful tools in treating behaviour disorders.

Assessment of the Drugs

The assessment of drugs which influence behavioural and emotional problems in a child is extremely difficult. It is important that no child should be on therapy which is doing him no positive good and which, possibly, has a dangerous side effect.

Family attitudes during drug administration can further complicate the operation. Some families hope the drug will be effective, while others are sceptical of the drug's effect and this will influence reports of the child's activities. Behaviour rating scales must therefore include therapists' and teachers' observations, as well as the family report.

Some attempt must be made to assess whether the drug is more effective than a placebo. In assessing the effects of drugs on behaviour, reports from both teachers and parents must be used. A behavioural rating, such as the teachers might be asked to fill in, is shown in Table 1. At the same time the parents are given a rating scale for hyperkinesis. These ratings evaluate seven points which describe the hyperkinetic impulse disorder. They include hyperactivity, short attention span and poor powers of concen-

tration, mood variability, impulsiveness, inability to delay gratification, irritability, explosiveness and poor school work. It is essential that the clinician himself should have a method for assessing these drugs and equally that the tests employed be as objective as possible. It is not difficult to devise such tests and the three we use are put forward not as ideals but merely as examples of what may be devised (Denhoff and Holden 1961). The three situations which we employ, designed to evoke body anxiety, are ring suspension, elevated board and centrifugal whirling.

Ring suspension: The child reaches for the gymnasium ring suspended five feet above the floor, while standing on a chair. When he is suspended by his arms the chair is removed from under him. Grasping strength, holding time and behavioural reaction are noted. Where the child demonstrates a very weak grasp, the therapist holds the child's hands on the rings during the evaluation of the test situation.
Elevated board: The child walks a plank six inches above ground, elevated at an angle of 45° from the floor. Walking rate, balance and behaviour are rated.
Centrifugal whirling: The child is blindfolded and placed on a revolving seesaw which is rotated for ten revolutions at a moderate speed. The effects of being blindfolded and rotated were observed and rated.

The child is observed in all three of these situations and an attempt made to estimate objectively his reaction to them (e.g., no anxiety, stiffening, trembling). We used an anxiety rating scale of 6 for each situation and had therefore an anxiety rating of 0 to 18. Other physicians can readily devise similar tests which will suit their own circumstances.

Amphetamine

Amphetamine (B-phenylisopropylamine) is a sympathomimetic amine in the same group of substances as adrenalin. Dextro-amphetamine (Dexedrine R) is twice as active pharmacologically as the racemic form (Benzedrine R). It is not surprising to find that its activities are related to those of adrenalin; for example, given intravenously, it increases the blood pressure and raises the heart's rate. Its central nervous activity is said to be the result of inhibition of the monoamine oxidases which break down adrenalin. Adrenalin and nor-adrenalin are present in the central nervous system in very low concentration, but comparable in amount to that found in the sympathetic nervous system. It is satisfactory to note that the highest concentration in the brain is in the diencephalon and, particularly, in the hypothalamus, and that amphetamine affects diencephalic function. In a normal person amphetamine acts as a potent stimulant of central nervous activity, increasing the level of alertness, decreasing fatigue and elevating the mood.

Paradoxically, in the presence of cerebral dysfunction, particularly of the diencephalic parts of the brain which may give rise to hyperkinesis, these drugs have a calming effect. Indeed, they counteract the symptoms of the hyperkinetic syndrome (Davidson *et al.* 1955). The child's new-found ability to keep his attention on things for longer periods is most striking. He is much more relaxed and in general easier to get along with. A dramatic alteration in the child's behaviour and in the parents' and teachers' attitudes towards the child may result.

TABLE 1.

Behaviour Rating Scale: The child is rated according to its usual behaviour compared with other children in the group.

Activity				
Full of energy; always constructively busy	Usually energetic (Somewhat more than average)	Acts well with group but is not spontaneous	Follows group action when reminded to do so	Lethargic; inert; needs many requests to act at all
Socialization				
Completely uninterested in group activity; prefers solitary play	Sometimes separates self from group	Belongs to group, but not outstanding	Fairly well accepted by group members	Extremely popular with group members
Fantasy				
Very unusual or strange talk or actions; peculiar; weird	Occasionally talks 'weird' but not often	Talks about 'jets' or 'monsters' but appropriately	Not very much interest in fantasy	Very down-to-earth; realistic; good planning
Group Integration				
Cannot delay what he wants; acts without adult consent	Needs group pressure to follow rest of group	Complies with group activity; sometimes helps when asked	Assists adult with group activity	Usually very helpful in organising activity; leader
Anxiety				
Extremely nervous or jittery (inappropriately)	Often tense and jittery	Ocasionally nervous but usually relaxed	Usually fairly relaxed and calm	Very relaxed; not startled or frightened even under tension
Distractibility				
Flits from one activity to another inappropriately	Quickly changes activities; easily bored	Stays at task for some time but likes to change	Continues an activity but may not always finish; fairly persistent	Remains at activity till satisfied of its completion; very persistent
Dependence				
Always asks for help, even when able to perform alone ('I can't do it')	Rather reliant on adult help	Asks for necessary help when needed	Sometimes needs help, but prefers to do it his own way	Expects to complete task without help ('I can do it')
Aggression				
Very cruel to other children, animals or objects whenever possible	Aggressive behaviour or rough talk to children or adults	Not outstandingly aggressive or passive	Tends to be picked on by others, but puts up some resistance	Often hurt by others; does not defend self
Mood				
Always joking; practical jokes; 'wild'; hardly ever serious	Usually happy; often smiling, likes jokes	Not unusually happy or unhappy; fairly stable mood	Sometimes quiet or unhappy but not too frequently	Extremely unhappy; tearful; sad; hard to console.

Side Effects

In our series no child has ever become addicted to the drug. As he grows older and bigger he may, of course, require higher doses. Occasionally the drug may become ineffective, in which case a switch to the other variety may be tried.

The children usually develop an 'amphetamine look' — a pale, pinched, serious facial expression with dark hollows under the eyes. This has no serious consequences, but the parents should be prepared for adverse comment about the child's appearance. The child may have difficulty in falling asleep and the appetite may be reduced for the first few weeks, but both these complications usually clear up spontaneously.

In some instances the drug may cause an increase in the components of the hyperkinetic syndrome, in which case it will have to be discontinued. In these cases there are also complaints of headache, epigastric distress and tremor of the fingers. These children are either extremely sensitive to the drugs, or their behaviour is not due to the hyperkinetic disorder syndrome.

Administration

Benzedrine and dexedrine are both available as a tablet and a long-acting capsule, while dexedrine is also available as an elixir. The effects of the drugs are apparent within twenty minutes of administration, fade in 3 or 4 hours and are gone within 12 hours. There is generally no carry-over effect. Administration after breakfast begins to fade by noon and is gone by the evening, and children with sleep disturbances of the hyperkinetic type may therefore require an evening dose. The tablet or the liquid have a more rapid and intensified action.

In a particular individual one of the two forms of drug may have either no effect or an unfavourable one, while the other form has beneficial effects. Or both may have favourable effects, but one may be better than the other. It is usual, therefore, to try both forms in each child.

Dosage is also highly individual. With children under 6 years we start with 5 mg. of racemic amphetamine or 2.5 mg. of dextro amphetamine, twice a day (after breakfast and after lunch). If this is not effective, the dose is doubled (10 mg. or 5 mg.) With children over 6 years we start with this higher dosage and increase in a week to 10 mg. of dextro-amphetamine or 20 mg. of racemic-amphetamine, if necessary. Occasionally higher doses are required and in our series the highest maintenance dose has been 20 mg. of dextro-amphetamine and 30 mg. of racemic-amphetamine daily. It may be necessary to give additional medication at different times of the day in particular children.

The action of the drug is highly specific for the hyperkinetic syndrome and has ineffectual or adverse effects in disturbances without an organic element. Many physicians have reported difficulties in the use of the drug and have had less satisfactory results than we have obtained. There are various reasons for this, but the most important is that both the parents and the physician have not fully appreciated the likely effects of the drug before administration. Thus, if too high a dosage is selected to start with and the child loses his appetite and suffers from sleeplessness, other beneficial effects are overlooked and the drug is prematurely withdrawn. Sometimes the

drug will not be of value therapeutically, but diagnostically it is valuable — the altered behaviour of the child demonstrates that the hyperkinetic syndrome is present.

Where amphetamine proves ineffective or has to be withdrawn because of the persistence of undesirable side effects, various newer preparations may be tried which are now briefly described before discussing drugs used in other emotional disorders.

Captodiamine (Suvren R). This drug is described as a non-hypnotic behaviour stabilizer which is helpful in stablizing the hyperkinetic behaviour of brain-damaged children. The dose (in tablet form) is 50 to 100 mg. three times a day.

It has not been the subject of a controlled study, but we have studied the effects of the drug on the Gastaut photometrazol test in five brain-damaged children. In four of the five cases there appeared to be a favourable beneficial effect on hyperkinetic behaviour associated with a rise of the photometrazol threshold level from abnormal to borderline abnormal or normal levels within a three day period after drug administration.

Dimethylaminoethanol Deanol (Deanol R). This drug is described as a psychic energizer. In a double blind study of seventy-five children with various emotional disturbances, Deanol was found useful in improving the child's skills and performance (Geller 1960). In another controlled study of epileptics versus non-epileptics with behaviour disorders, the drug was found useful in improving learning skills in non-epileptic children (Livingston 1954). We have used the drug in non-controlled office studies in children where the electro-encephalogram has been normal, and where amphetamine could not be tolerated. With 300 mg. at breakfast daily for three weeks and then 100 mg. daily thereafter, there has appeared to be improved school performance. In half of the cases when medication is stopped after three months, school improvement continues. In the remainder, there has been a regression in learning skills. However, a drug placebo study indicated no statistical difference with deanol in learning or behaviour effectiveness (Kugel and Alexander 1963).

Reserpine and Methylphenidate (Serpatilin R). This tablet, which combines the calming action of serpasil and the antidepressant action of ritalin is worthy of mention. In doses of 10 mg. two or three times a day, hyperactive brain-damaged mentally-retarded children have been calmed sufficiently to make it possible to place them in the classroom. While controlled studies have not been done, there has been sufficient experience with individual cases to recommend a trial of this drug for mongoloids and other mentally retarded children where hyperactivity presents a problem. It is available in tablets which each contain 0.1 mg. of serpasil and 10 mg. of ritalin.

Phenothiazine Derivatives.

These drugs, which have been extensively developed over the last 15 years, are an important aid in the treatment of emotional disorders of cerebral palsy. The best known member of this group is chlorpromazine (Thorazine or Largactil R), but there are many others — thioridiazine (Mellaril R), fluphenazine (Permitil R), prochlorperazine (Compazine R), trifluoperazine (Stelazine R), triflupromazine (Vesprin R), and promazine (Sparine R). The group is believed to act on the reticular substance of the central nervous system, particularly in the hypothalamic area. The group may be of value

both in the hyperkinetic behaviour disorder syndrome and in other behavioural disorders of childhood. They are strikingly effective in fear and panic reactions. One observes in the children an inner quietening and improved responsiveness to individuals.*

Toxic Effects

In those with a lowered threshold for convulsions due to brain damage, chlorpromazine may precipitate a seizure. As many C.P.s have seizures this is a serious drawback to the use of the drug in cerebral palsied children. Other side effects are hypotension, listlessness and the development of Parkinson-like features, — mask facels, increased tremors with loss of co-ordination of fine motor movements. Jaundice and agranulocytosis can occur in adults but are very unusual in children. Exfoliative dermatitis and erythematous eruption of the face and eyes are not uncommon, particularly when the children are exposed to sunlight. (Parents should be warned of this effect).

Administration

Chlorpromazine is the drug of choice and is usually prescribed in doses of 10-25 mg. three times a day. Of the other drugs in the group Stelazine, Vesprin and Sparine often make a child too drowsy. With Compazine the margin between a therapeutic dose and toxicity is too small and the drug may increase athetosis and tremors where these symptoms exist. Permitil (10 mg. three times daily) seems to be the best alternative to chlorpromazine.

Where chlorpromazine is to be administered despite the presence of convulsions it can be given together with an anticonvulsant. In hyperkinetic disorders it may be valuable to prescribe it with dexedrine (5 to 10 mg. of dexedrine and 10 to 25 mg. of chlorpromazine three times daily).

Hypnotics

In view of the side effects of the barbiturates they are best avoided in the treatment of sleep disturbance and sleep resistance. Promethazine (Phenergan)R is the drug of choice, as not only is it usually effective as a hypnotic, but the drug often has a tranquillizing effect as well. We use relatively large doses such as a teaspoonful of Phenergan Fortis Syrup at bedtime (this is approximately 25 mg.). If this is ineffective, then trimeprazine tartrate (Temaril)R in 5 mg. or 10 mg. dosage at bedtime has proved to be of value. Chloral hydrate is another well known and effective remedy which we use when we envisage only a short period of therapy.

Appetiser

In poor appetite problems an equal amount of high potency B12 and B1 vitamins (Trophite Liquid) and Elixir Reserpine (Serpasil) 0.2 mg. per teaspoonful, in combination, seems to improve the appetite. Periactan Syrup also appears to potentiate appetite in these children.

*Thioxanthene (Taractan)R, a new preparation which is not a phenothiazine, is said to have powerful tranquilising effects similar to chlorpromazine.

Vitamins

Most of the vitamins have a definite action on the C.N.S. in man and recent evidence suggests that the role of amino acid (McIlwain 1959) has been underestimated. We lack at the moment any controlled studies of the value of these substances which may well have important effects in infants recovering from cerebral damage such as anoxia.

Thiamine depletion produces a neurasthenic syndrome with irritability, lassitude and anorexia, as well as electro-cardiographic changes, muscle tenderness and lowered basal metabolic rate with intolerance to cold. A more severe depletion can result in ophthalmoplegia, peripheral neuropathy, ataxia and clouding of consciousness.

Nicotinic acid depletion can be associated with schizoid behavioural reactions, and in disturbed children with depression, dizziness, insomnia and morbid fear one may find the administration of 100-300 mg. of nicotinamide three times a day favourably alters the adverse behaviour characteristics which are usually attributed to childhood autism and/or amentia. Thus it is a wise decision to prescribe nicotinic acid or nicotinamide as a diagnostic or early therapeutic agent when a child is seen who is primarily believed to be psychotic. I have also used nicotinamide (50-100 mg.) three times a day in cases of anoxia of the newborn and early infancy for the vasodilator action on cerebral blood vessels with the hope of stimulating cerebral depression.

Pyridoxine depletion results in convulsions. In unusual instances, it has been found that infants can be pyridoxine-dependent. Without a dose of at least 1.5 mg. of pyridoxine per day, abnormal electroencephalograms will result along with generalised intractible convulsions.

A central nervous effect is also known to occur with vitamin B12 deficiency, and in pernicious anaemia there is a mental confusion and other evidences of mental depression. Electro encephalographic changes can occur independently of the erythrocyte changes, and not secondary to the anaemia.

A variety of central nervous system effects can occur with deficiences of pantothenic acid, riboflavin and other vitamins.

While these various metabolic syndromes are not commonly associated with cerebral palsy, it is wise to remember that severely handicapped children or those who are resistant to or incapable of eating sufficient food can be subject to such a deficiency without recognition of the presence of such a depletion.

Amino acids. Amino acids constitute 40 per cent of the dry weight of the brain. Disturbances of amino acid metabolism must be considered in cerebral palsy. In an unpublished study (Denhoff 1962), there was evidence of increased generalised amino aciduria in cases of athetosis and in cases of epilepsy. The brain utilizes glutamic acid plus glutamine and gamma aminobutyric acid more than other amino acids. Clinical use of glutamic acid has been disappointing, but it is occasionally useful in the control of petit mal attacks. In hypoglycaemic coma, the administration of glutamic acid intravenously will restore consciousness more readily than intravenous glucose alone.

The recent discovery of numerous clinical entities in which amentia, convulsions and other neurological abnormalities are part of the picture emphasizes the role that disturbed amino acid metabolism plays in neurological disorders. Dietary manipulation promises to play a large part in the prevention of these conditions. However, it is

likely that specific agents, such as the chelating agent, penicillamine, used in Wilson's disease (hepato-lenticular degeneration), may be found to be of value in other of these disorders which affect mental growth and development.

Hormones

Pituitary hormones must be thought of when treating cases of cerebral palsy. There is little direct evidence that hormones have specific value in the treatment of cerebral palsy, but many body functions are related to metabolism of the hypothalamus and related structures, and in cerebral palsy 20 per cent or more cases have delayed bone age.

Thyroid hormone or triiodothyronine (Cytomel R) rarely proves to be of clinical value, but occasionally, when triiodothyronine (Cytomel) is used cautiously, there is improvement in constipation and tissue turgor. Borderline protein iodine levels are found in a few cases (Denhoff and Solomons, 1958).

REFERENCES

Davidson, D. T., Jr., Lombroso, C., Markham, C. H. (1959) 'Methylphenyl-succinimide (Milontin) in epilepsy.' *N. E. J. Med.*, **252**, 173-175.

Denhoff, E. (1962) Unpublished data presented at 2nd. Annual Research Day, Miriam Hospital, Rhode Island, U.S.A.

——, Holden, R. H. (1961) 'Relaxant drugs in cerebral palsy: 1949-1960.' *N. E. J. Med.*, **264**, 475.

——, Solomons, G. (1958) Exhibit: 'Triiodothyronine (Cytomel) in cerebral palsy.' Rhode Island; American Acad. Cerebral Palsy.

Doyle, P. J. (1962) 'The organic hyperkinetic syndrome.' *J. School Health*, **30**, 299-306.

Gastaut, H. (1950) 'Combined photic and Metrazol activation of the brain.' *Electroenceph. clin. Neurophysiol.*, **2**, 249.

Geller, S. J. (1960) 'Comparison of a tranquilizer and a psychic energizer'. *J.A.M.A.*, **174**, 481-484.

Kugel, R. B., Alexander, T. (1963) 'The effect of a central nervous system stimulant (Deanol) on behaviour.' *Pediatrics*, **31**, 651-655.

Laufer, M. W., Denhoff, E. (1957) 'Hyperkinetic behaviour syndrome in children.' *J. Pediatrics*, **50**, 463-474.

——, ——, Rubin, E. L. (1954) 'Photometrazol activation in children.' *Electroenceph. clin. Neurophysiol.*, **6**, 1-8.

Livingston, S. (1954) The Diagnosis and Treatment of Convulsive Disorders in Children. Springfield, Illinois: Thomas.

Mc Ilwain, H. (1959) Biochemistry and the Nervous System. 2nd. ed. Boston, Mass: Little, Brown and Co.

CHAPTER 9

Toxic Drug Reactions

ERIC DENHOFF

Whether an anticonvulsant, psychotropic, or muscle relaxant drug is prescribed, it is important to have a practicable plan to prevent toxic drug reactions. Drug reactions are generally the result of individual idiosyncrasy and may occur regardless of drug dosage. The immediate reactions which can be clinically observed (such as ataxia, skin rash, gastro-intestinal upsets, or lethargy) usually occur within the first 2 weeks of drug administration. The onset of hematologic, liver and renal complications is more insidious, but they usually appear within three months after the administration of a new drug. Patients who are able to tolerate a drug during this period can normally take the drug for years with no adverse reaction, providing the dosage is not increased beyond the bounds of propriety. The plan outlined below should be followed if serious consequences are to be avoided.

A complete blood count and urine analysis are carried out before administration of the drug. Two weeks later a haemoglobin and differential smear is checked with an additional red blood cell count and white blood cell count if there are clinical or laboratory signs of drug toxicity. Urine should be examined for albumin, urobilinogen, and, microscopically, for red cells.

The immediate adverse reactions to be observed by these tests are the drop of haemoglobin below 10.0 g/%, and/or the shift of the normal distribution of leukocytes to an increased proportion of lymphocytes, some of which appear atypical. Also, the platelets may now be relatively few. The patient is not usually examined at this stage, but if the above findings are present an examination is necessary to check for clinical signs of anemia, jaundice and hepatosplenomegaly. A sphygmomanometer cuff is applied with pressure and the presence of petechiae is checked (or use a petechiometer). Such findings at 2 weeks imply drug toxicity and withdrawal is indicated. Similarly, an increase of urine urobilinogen beyond a dilution of 1:30 may imply early liver dysfunction resulting from the drug, and the drug should be withdrawn.

The white blood cell count is checked for evidence of abnormal reduction and if the value is below 5000 white blood cells per cu. mm. a bone-marrow aspiration is performed to make sure that there is no granulocyte reduction with replacement by lymphocytes and mononuclear cells. The bone-marrow aspiration is a valuable predictive tool, particularly with such drugs as Phenurone (Denhoff and Robinault 1960). It can be done in the office. A small, undiluted sample is obtained by simple aspiration below the crest of the ilium and a thinly stained smear is made. There are two changes to observe which may prevent serious hematological complications. The first is an early loss of multilobulated granulocytes and an increase in mononuclear cells. If the young granulocytes are over 26 per cent of a total of 200 cells counted, there will be

no difficulty. Should they fall below this level, however, subsequent agranulocytosis may develop and drug withdrawal is imperative.

Any decline in the number of megakaryocytes in the preparation should also be noted. This is potentially serious if the megakaryocytes are unsegmented and may be predictive of purpura hemorrhagica, which is also a sign for drug withdrawal.

Usually no complications are found in the 2-week period and the patient is asked to return in a month. Then a haemoglobin, white count, and differential (including platelets from the stained smear) are repeated. A routine urine, including a urinary urobilinogen, is also tested. Where there are suspicious findings a bone-marrow aspiration is needed.

The danger period for serious blood and urine reactions is between the first and third month of therapy. During this period a liver function test, such as the thymol turbidity, will give valuable information as to possible liver damage. If this is abnormal then a battery of liver function tests are indicated.

The urine may show 4-5 red blood cells per high power field (especially with trimethadione). This need not cause concern. However, the urine examination should be repeated weekly, and evidence of increasing pathology indicates drug withdrawal. In our experience nephrosis is not of sudden onset but is rather the consequence of prolonged 'trace albuminuria' and hematuria.

It is remarkable how little pathology one finds in most children who receive known toxic drugs and new drugs of possible toxicity. This may be a reason why many children do not receive an adequately planned follow-up programme. There are other reasons—for example, because the parents do not realise the potential seriousness of drug ingestion they fail to report to the doctor. The plan I have presented gives good protection, good prediction, is not too expensive and should not produce too much anxiety in the patient or his parents.

When the child takes drugs longer than the 3-month 'danger' period, a haemoglobin and a stained blood smear and routine urine test every 2-3 months will suffice to minimize difficulty. Nevertheless, meticulous attention must be paid to loss of or appearance of granulocytes in the stained smear, for such a shift is often a sign of trouble.

REFERENCE

Denhoff, E., Robinault, I. R. (1960). Cerebral Palsy and Related Disorders. McGraw-Hill: New York.

Drug Index

In this table the generic name of the drug is listed in the first column. A chemical formula is given underneath this. The trade names are given in column two. All trade names are cross-referenced in an index immediately following this table and the generic name may be identified if the reader knows only the trade name. The main indication for the use of the drug in cerebral palsy is given in column three: many of the drugs, however, may have other important effects. Thus, many muscle relaxants may also affect behaviour. In column four a dose is given, usually daily, for suggested optimal value in the 5-10 year range. (Many of the drugs will be administered in a divided dose and, initially, in smaller quantity and the physician should, in all instances, confirm the suggested doses with the manufacturers recommendations). Column five gives page numbers to text reference to the drug. This table is not complete, but is reasonably comprehensive and will, we hope, prove of some value. A number of sources has been consulted, chiefly the *Physicians' Desk Reference* (Medical Economics Inc., 1964) and the *International Dictionary of Drugs used in Neurology and Psychology* by C. M. Poser (Thomas, 1962).

Generic Name	*Trade Name*	*Indications*	*Dose*	*Page*
Acetazolamide 5-acetamino-2-sulphamoyl-1, 3, 4-thiadiazole	Acetazoleamide, Diacarb, Diakarb, Diamox, Diluran, Diomax, Direnil, Direx, Diural, Diuretex, Diuribeta, Diuriwas, Diutazol, Edemox, Eumicton, Fonurit, Ledamox, Natrionex, Odemin.	Epilepsy	Approx. 500 mgms. daily	60
Aminoglutethimide 2-(*p*-aminophenyl)-2-ethylglutarimide	Ciba 16038, Elipten, Elyptene	Epilepsy	Up to 750 mgms. daily	60
Amphetamine (±)-2-amino-1-phenylpropane	Actemin, Adipan, Adiparthrol, Aktedron, Alentol, Allodene, Amfetamine, Amitrene, Amphamed, Amphätamin, Amphate, Amphedrine, Amphoids, Anfetamina, Benzafinyl, Benzadrina, Benzedrine, Benzedryna, Benzpropamine, Betafen, Centramina, Dextro-profetamine, Dietamine, Dopamine, Durophet, Elastonin, Elastonon, Euphodine, Fenamin, Fenedrin, Fenopromin, Ibiozedrine, Isamin, Isoamyne, Isomyn, Leodrin, Levonor, Linampheta, Mecodrin, Monetamine, Monophos, Norephedrane, Ortedrine, Orthedrin, Pharmamedrine, Phenamine, Phenedrine, Phenpromin, Profamina, Profetamine, Propisamine, Psychedrine, Psychedryna, Psychoton, Racephen, Raphetamine, Simpamina, Simpatedrin, Stimulan, Sympametin, Sympamine, Sympatedrine.	Behavioural States	Up to 20 mgm. daily	16,17,18,19, 20,60,64,65, 67,68
Captodiame *P*-butylthiodiphenylmethyl-2-dimethylaminoethyl sulfide	Captadiamine, Covatine, Covatix, Suvren.*	Behavioural States	Up to 30 mgm. daily	68
Carisoprodol *N*-isopropyl meprobamate	Apesan, Carisoma, Carisoprol, Rela, Sanoma, Soma, Somadril, Somalgit, Somanil.	Muscle Relaxant	Up to 2 g. daily	27,43,45,46, 49
Chloral Hydrate trichloroacetaldehyde monohydrate	Aquachloral, Chloraldurat, Felsules, Hydral, Hydrat Chloralu, Khloralgidrat, Lorinal, Lycoral, Mechloral, Medianox, Noctec, Phaldrone, Rectules, Somnos, Sontec, Sorosil, Wodan chloralu, Wodnik chloralu, Wodzian chloralu.	Hypnotic States	5 to 10 grs. nocte	69
Chlordiazepoxide 7-chloro-2-methylamino-5-phenyl-3*H*-1, 4-benzodiazepine-4-oxide	Librium, Metaminodiazepossido, Methaminodiazepoxide, Reliberan, Seren Vita, Sonia.	Muscle Relaxant Behavioural States	Up to 30 mgms. daily	27,43,44,46, 47,48,50
Chlormezanome 2-(4-chlorophenyl)-3-methyl-4-metathiazanone-1, 1-dioxide	Banabin, Chlormethazanone, Fenarol, Muskel, Rilaquil, Trancopal.	Muscle Relaxant	Up to 400 mgms. daily	27
Chlorpromazine 2-chloro-10-(3-dimethlyaminopropyl) phenothiazine	Aminazine, Ampliactil, Ampliactyl, Amplictil, Chlorbromasin, Contomin, Hibanil, Hibernal, Klopromex, Largactil, Largaktil, Largaktyl, Megaphen, Neuropromazin, Novomazina, Opromazin, Promactil, Promazil, Propaphenin, Prozil, Thorazene, Thorazine, Torazina, Wintermin.	Behavioural States	Up to 75 mgms. daily	3,16,27,45, 68,69

*No longer available

Chlorzoxazone 5-chloro-2-benzoxazolidone	Chloroxazone, Miotran, Neoflex, Paraflex, Solaxin	Muscle Relaxant	Up to 500 mgms. daily	43
Cycrimine 1-cyclopentyl-1-phenyl-3-(1-piperidyl)-1-propanol	Cicrimina, Pagitane.	Muscle Relaxant	Up to 5 mgms. daily	26
Deanol 2-dimethylaminoethanol	Atrol, Deaner, Dianol, Dienol, Dimethaen, Pabenol, Recrein.	Behavioural States	Up to 100 mgm. daily	68
Dexamphetamine (+) amphetamine	Adjudets, Adrizine, Afatin, Afettine, Albemap, Am-dex, Amitrene, Amphedrine, Ampherex, Amphex, Amsustain, Betafedrina, d-Betaphedrine, Carrtime, Dadex, D-Amfetasul, D.A.S., D-Ate, D-Citramine, Dephadren, Desoxyne, Dexaline, Dexalme, Dexalone, Dexamed, Dexedrina, Dexedrine, Dexoval, Dex-sule Dexten, Dextenal, Dextro-anfetamina, Dextro-profetamine, Dextrosule, Diocurb, Domafate, Dynaphenyl, Elastonon, Ephadren, Evrodex, Hetamine, Lentanet, Maxiton, Obesedrin, Obesonil, Pellcaps, Phenpromin, Phetadex, Proptane, Revidex, Simpamina-D, Sympamin, Synatan, Tanphetamine, Tempodex, Zamine.	Behavioral States	Up to 10 mgms. daily	64,65,67
Diazepam 3-dihydro-1-methyl-5-phenyl-2H-1	Valium.	Muscle Relaxant	5 mgms. t.d.s.	27,43,44,47, 48,49
Diethylpropanediol 2, 2-diethyl-1, 3-propanediol	Prenderol, Prendiol.	Muscle Relaxant Epilepsy	Up to 750 mg. daily	27
Emylcamate diethyl methyl carninol urethan	Nuncital, Striatran	Muscle Relaxant	Up to 300 mgms. daily	43,45
Ethosuximide 3-ethyl-3-methyl-pyrrolidine-2, 5-dione	Emeside, Ethosuccinimide, Petnidan, Suxinutin, Zarontin	Epilepsy	Up to 500 mgms. daily	59,60
Ethotoin 3-ethyl-5-phenyl- hydantoin	Nirvanol, Peganone	Epilepsy	Up to 1.5 g. daily	56
Fluphenazine 10-(3-[4-(2-hydroxyethyl) piperazin-1-yl](propyl)-2-trifluoromethylphenothiazine)	Anatensil, Anatensol, Flumezin, Lyogen, Moditen, Omca, Pacinol, Permitil, Prolixin, Sevinol, Siqualine, Tensofin, Trancin, Vespazine.	Behavioural States	Not more than 1 mgm. daily	8,68,69
Hydrazino dyethyl triazine	Ciba 13155	Muscle Relaxant	Not available	43

Generic Name	*Trade Name*	*Indications*	*Dose*	*Page*
Hydroxyphenamate 2-hydroxy-2-phenyl-butyl carbamate	Listica	Muscle Relaxant	Up to 500 mgms. daily	43
Hydroxyzine 1-(*p*-chlorobenzhydryl)-4-[2-(2-hydroxyethoxy)etyl] piperazine	Atara, Atarax, Aterax, Idrossizina, Masmoran, Placidol, Tran-Q.	Behavioural States	50-100 mgms. daily	27,8
Imipramine 2, 2-(3-dimethylaminopropylimino) bibenzyl.	Deprinol, Imizin, Promiben, Surplix, Tofranil.	Behavioural States	Up to 75 mgms. daily	3,8
Mephenytoin 5-ethyl-3-methyl-5-phenylhydantoin	Convulsan, Epilan, Epilunal, Epital, Gerol-Epilan, Insulton, Mephenetoin, Mesantoin, Mesontoin, Methantoin, Methoin, Methylnirvanol, Methylphenetoin, Metydan, Phenantoin, Sacerno, Sedantoin, Sedantoinal, Triantoin.	Epilepsy	Up to 500 mgms. daily	16,56
Meprobamate 2, 2-di (carbanoyloxymethyl) pentane	Amepromat, Andaxin, Aneural, Ansietan, Ansil, Apascil, Artolon, Atraxin, Biobamat, Calmax, Calmiren, Cirpon, Cirponyl, Cyrpon, Dapaz, Diveron, Dormabrol, Ecuanil, Epikur, Equanil, Equatrate, Equinil, Equitar, Gagexyl, Harmonin, Holbamate, Madiol, Margonil, Mepantin, Mepavlon, Mepranil, Meprin, Meprobam, Meproban, Meprodil, Meprosin, Meprospan, Meprotabs, Meprotan, Meprozine, Miltamato, Miltaun, Miltown, Morbam, Neo-Tran, Nervonus, Oasil, Orolevol, Panediol, Pan-Tranquil, Paxin, Perequil, Perquietil, Pertranquil, Placidon, Prequil, Probamato, Probamyl, Procalmadiol, Procalmidol, Procarbamide, Proquanil, Quaname, Quanil, Reostral, Restenil, Restinal, Restinil, Sedanyl, Sedazil, Setran, Shalvaton, Sowell, Tensol, Tensonal, Tranquil, Tranquiline, Tranquisan, Trelmar, Urbil.	Muscle Relaxant Epilepsy	Up to 1.2 g. daily	25,27,43,44, 45
Metaxalone	Skelaxin	Muscle Relaxant	Approx. 100 mgms. daily	27,43
Methaminobenzodioxan	Quilaflex	Muscle Relaxant	Not available	43
Metharbital 5, 5-diethyl-1-methyl barbituric acid.	Endiemal, Gemonal, Gemonil, Gemonit, Metabarbital, Methabarbital.	Epilepsy	Up to 300 mgms. daily	16,54,58
Methocarbamol guaiacol glycerylether carbamate	Etroflex, Guaiphenesin carbamate, Metocarbamol, Miowas, Neuraxin, Robaxin, Robaxon, Tresortil.	Muscle Relaxant	Up to 400 mgms. daily	27,43

Methylphenobarbital 5-ethyl-1-methyl-5- phenyl-barbituric acid	Barbiphenal, Enphenemal, Femiton, Isonal, Mebaral, Mebarol, Mefenal, Mefenalettae, Meforbarbital, Mephobarbital, Phemitone, Prolamine, Prominal, Promitone	Epilepsy	Up to 60 mgms. daily	58
Orphenadrine *O*-methyldiphenyhydramine	Brocadisipal, Disipal, Mefenamina, Mephenamine, Myophane, Norflex, Orphenadril, Parekin, Phasein.	Muscle Relaxant	Approx. 100 mgms. daily	27,43
Paramethadione 3-ethyl-5, 5-dimethyloxazolidine-2, 4-dione	Isoethadione, Paradione	Epilepsy	Up to 60 mgms. daily	57
Pentobarbital 5-ethyl-5-(1-methylbutyl) barbituric acid	Auropan, Barbityral, Barpental, Bevital, Carbrital, Dorsital, Embutal, Etaminal, Ethaminal, Isomytal, Isobarb, Iturate, Mebubarbital, Mebumal, Napental, Nembutal, Paiapent, Panbule, Pembules, Pentale, Pentobarbitone, Pentobrocanol, Pento-Del, Pentone, Pentyl, Repocal, Sagatal, Sombutal, Sopental, Sotyl.	Sleep Disturbance	Up to 150 mgms. daily	11
Phenacemide 1-(2-phenyl) acetylurea	Acetylureum, Carbanmide, Cetylureum, Comitiadon, Eferon, Epiclase, Fenacemid, Fencetil-Karbamid, Fenilep, Fenostenyl, Fenurone, Neophedan, Phacetur, Phenacereum, Phenacetur, Phenalum, Phenicarb, Phenurone, Phenutal, Phenyrit, Phetylureum, Trioxanona.	Epilepsy	Up to 1.5 gm. daily	14,57,59
Phenobarbital phenylethyl barbituric acid	Adonal, Aephenal, Agrypnal, Agrypnaletten, Amylofene, Aphenylbarbit, Aphenyletten, Austrominal, Barbapil, Barbellen Barbenyl, Barbilettae, Barbiphen, Barbiphenyl, Barbipil, Barbita, Barbivis, Betal, Bialminal, Blu-Phen, Calmetten, Cardenal, Cemalonol, Dezibarbitur, Dormiral, Dormytal, Dorsital, Duneryl, Epanal, Epidorm, Eskabarb, Etilfen, Euneryl, Fenemal, Fenobarbital, Fenobarbitalio, Fenobarbiton, Fenobarbitoon, Gardenal, Gardepanyl, Gargenal, Hypnalet-ten, Hysteps, Leonal, Lepinal, Linasen, Liquital, Lixophen, Luminal, Molinal, Neurobarb, Nevrotamine, Nirvonal, Noptil, Numol, Nunol, Phenaemal, Phenemal, Phenobal, Phenobarbitone, Phenobarbyl, Phenonyl, Phenoturic, Phenylbarbital, Phob, Seda-Ped, Sedocentillen, Sevenal, Sodico-W, Somnolens, Somnoletten, Somnosan, Somonal, Spasepilettan, Spasepilin, Starifen, Starilettae, Stental, Teolaxin, Versomnal.	Epilepsy	Up to 65 mgms. daily	16,44,53 54, 58
Phensuximide *N*-methyl-2-phenyl-succinimide	Epimid, Fensuximide, Lifene, Milontin, Milonton, Succitimal	Epilepsy	Up to 1.5 g. daily	60
Phenyramidol a-(2-pyridylaminomethyl) benzyl alcohol	Analexin.	Muscle Relaxant	Up to 400 mgms. daily	27,43

Generic Name	*Trade Name*	*Indications*	*Dose*	*Page*
Phenytoin 5, 5-diphenylhydantion	Alepsin, Aleviatin, Antilepsin, Anti-sacer, Auranile, Cansoin, Citrullamon,Citrulliamon, Comital, Comitoina, Denyl, Difenin, Difhydan, Di-hydan, Dihydantoin, Dilantin, Dillantin, Dintoin, Diphantoine, Diphedal, Diphedan, Diphenin, Diphentoin, Diphenylan, Epamin, Epanutin, Epelin, Epifenyl, Epilan, Epilantin, Epinat, Eptal, Eptoin, Fenantoin, Fenitoina, Fentoin, Fenytoine, Gerot-Epilan, Hidantal, Hidantina, Hydantal, Hydantin, Hydantoin, Hydantoinal, Idantoil, Idantoin, Lepitoin, Minetoin, Neos-hidantoina, Om-Hydantoine, Oxylan, Phanantine, Phenantoin, Silantin, Sodantoin, Sodanton, Solantin, Solantoin, Solantyl, Tacosal, Toin, Zentropil.	Epilepsy	3 g. daily	14,15,25,54, 55,56,58
Primidone 2-desoxyphenobarbituric acid	Desoxyphenobarbitone, Geksamidan, Hexamidine, Mylepsin, Mysoline, Primaclone.	Epilepsy	Up to 750 mgms. daily	16,43,44,53, 56,57,59
Prochlorperazine 3-chloro-10-[3-(4- methyl-piperazinyl) propyl] phenothiazine	Capazine, Chlormeprazine, Compazine, Nipodal, Novamin, Prochlorpemazine, Proclorpemazina, Stementil, Stemetil, Tementil.	Behavioural States	Not more than 1 mgm. daily	68,69
Procyclidine 1-cyclohexyl-1-phenyl-3-pyrrolidino-1-propanol	Kemadrin, Metanin, Vagosin.	Muscle Relaxant	Approx. 10 g. daily	26
Promazine 10-(3-dimethylamino-propyl) phenothiazine	Ampazine, Apacergil, Centractil, Eliranol, Esparin, Lemazina, Liranol, Neo-Hibernex, Prazine, Promacina, Promanyl, Promazinon, Promwill, Propazin, Protactyl, Pro-Tran, Sediston, Sparine, Starazine, Talofen, Verophen.	Behavioural States	Approx. 75 mgms. daily	68
Promethazine 10-(2-dimathylamino-propyl) phenothiazine	Atosil, Avomine, Dimapp, Diprazin, Diprozin, Fargan, Fenazil, Fenergan, Hiberna, Isophenergan, Isopromethazine, Lergigan, Phenergan, Pipolphen, Proazimine, Procit, Promazinamid, Promezathine, Protazine, Prothazin, Pyrethia, Tanidil, Thiergan, Vallergin.	Hypnotic States	Up to 25 mgms. nocte	69
Sodium Bromide	Neurosine (contains other bromides), Sedobromal,	Epilepsy Hypnotic States	Up to 1 g. daily	25,59,60
Styramate 2-hydroxyphenethyl carbamate	Linaxar, Sinaxar.	Muscle Relaxant	Approx. 500 mgms. daily	27,43
Thioridazine 10-[2-(1-methypiperid- 2-yl) ethyl)]2-methylthio-phenothiazine	Mallorol, Malloryl, Meleril, Mellaril, Mellerettes, Melleril.	Behavioural States	Up to 75 mgm. daily	68

Trifluoperazine 2-trifluomethyl-10 [3-(1-methyl-4-piperazinyl) propyl] phenothiazine	Eskazine, Jatroneural, Stelazine, Terfluzin.	Behavioural States	Up to 30 mgms. daily	68,69
Trifluopromazine 2-triflouromethyl- 10- (3- dimethylamino-propyl) phenothiazine	Adazine, Esprivex, Flumazin, Fluomazina, Fluopromazine, Fluorofen, Psyquil, Siquil, Vespral, Vesprin.	Behavioural States	Approx. 50 mgms. daily.	68,69
Trihexyphenidyl 1-cyclohexyl-3-(1-piperidyl)-1-phenyl-1-propanol.	Artane, Benzhexol, Hexyphenidyl, Pacitane, Paralest, Pargitan, Parkinsan, Partigan, Peragit, Pipanol, Triexifenidila, Triphenidyl.	Muscle Relaxant	5 mgms. daily	26
Trimeprazine Tartrate	Temaril.	Hypnotic States	Up to 10 mgms. nocte	69
Trimethadione 3, 5, 5-trimethyloxazolidine-2, 4-dione	Absentol, Absetil, Convexina, Edion, Epidion, Epidon, Etydion, Minoaleviatin, Petidion, Petidon, Petilep, Petimalin, Ptimal, Tridilona, Tridione, Trilidona, Trimedal, Trimedone, Trimetadione, Trimetin, Trioxanona, Triozanona, Troxidone,	Epilepsy	Up to 600 mgms. daily	14,57,58
Tropigline 2-methyl-2-butenoyltropine	Tigliodine, Tiglyl tropine, Tropine tiglate	Muscle Relaxant	Not available	43
Zoxazolamine	Contrazole, Deflexol, Flexin, Zoxamin.	Muscle Relaxant	Up to 750 mgm. daily	27,43,45

Trade Names with Reference to Generic Names

A	
Absentol	Trimethadione
Absetil	Trimethadione
Acetazoleamide	Acetazolamide
Acetylureum	Phenacemide
Actemin	Amphetamine
Adazine	Triflupromazine
Adipan	Amphetamine
Adiparthrol	Amphetamine
Adjudets	Dexamphetamine
Adonal	Phenobarbital
Adrizine	Dexamphentamine
Aephenal	Phenobarbital
Afatin	Dexamphetamine
Afettine	Dexamphetamine
Agrypnal	Phenobarbital
Agrypnaletten	Phenobarbital
Aktedron	Amphetamine
Albemap	Dexamphetamine
Alentol	Amphetamine
Alepsin	Phenytoin
Aleviatin	Phenytoin
Allodene	Amphentamine
Am-Dex	Dexamphetamine
Amepromat	Meprobamate
Amfetamin	Amphetamine
Aminazine	Chlorpromazine
Amitrene	1. Amphetamine, 2. Dexamphetamine
Ampazine	Promazine
Amphamed	Amphetamine
Amphatamin	Amphetamine
Amphate	Amphetamine
Amphedrine	1. Amphetamine, 2. Dexamphetamine
Ampherex	Dexamphetamine
Amphex	Dexamphetamine
Amphoid-S	Amphetamine
Ampliactil	Chlorpromazine
Ampliactyl	Chlorpromazine
Amplictil	Chlorpromazine
Ansustain	Dexamphetamine
Amylofene	Phenobarbital
Analexin	Phenyramidol
Anatensil	Fluphenazine
Anatensol	Fluphenazine
Andaxin	Meprobamate
Aneural	Meprobamate
Anfetamina	Amphetamine
Ansietan	Meprobamate
Ansil	Meprobamate
Antilepsin	Phenytoin
Anti-Sacer	Phenytoin
Apacergil	Promazine
Apascil	Meprobamate
Apesan	Carisoprodol
Aphenylbarbit	Phenobarbital
Aphenyletten	Phenobarbital
Aquachloral	Chloral hydrate
Artane	Trihexyphenidyl
Artolon	Meprobamate
Atara	Hydroxyzine
Atarax	Hydroxyzine
Aterax	Hydroxyzine
Atosil	Promethazine
Atraxin	Meprobamate
Atrol	Deanol
Auranile	Phenytoin
Auropan	Pentobarbital
Austrominal	Phenobarbital
Avomine	Promethazine
B	
Banabin	Chlormezanone
Barbapil	Phenobarbital
Barbellen	Phenobarbital
Barbenyl	Phenobarbital
Barbilettae	Phenobarbital
Barbiphen	Phenobarbital
Barbiphenal	Methylphenobarbitol
Barbiphenyl	Phenobarbital
Barbipil	Phenobarbital
Barbita	Phenobarbital
Barbityral	Pentobarbital
Barbivis	Phenobarbital
Barpental	Pentobarbital
Benzafinyl	Amphetamine
Benzedrina	Amphetamine
Benzedrine	Amphetamine
Benzedryna	Amphetamine
Benzhexol	Trihexyphenidyl
Benzpropamine	Amphetamine
Betafedrina	Dexamphetamine
Betafen	Amphetamine
Betal	Phenobarbital
d-Betaphedrine	Dexamphetamine
Bevital	Pentobarbital
Bialminal	Phenobarbital
Biobamat	Meprobamate
Blu-Phen	Phenobarbital
Brocadisipal	Orphenadrine
C	
Calmax	Meprobamate
Calmettan	Phenobarbital
Calmiren	Meprobamate
Cansion	Phenytoin
Capazine	Prochlorperazine
Captadiamine	Captodiame
Carbanmide	Phenacemide
Carbrital	Pentobarbital
Cardenal	Phenobarbital
Carisoma	Carisoprodol

Carrtime	Dexamphetamine
Cemalonol	Phenobarbital
Centractil	Promazine
Centramina	Amphetamine
Cetylureum	Phenacemide
Chloraldurat	Chloral hydrate
Chlorbromasin	Chlorpromazine
Chlormeprazine	Prochlorperazine
Chlormethazonone	Chlormezanone
Chloroxazone	Chlorzoxazone
Ciba 13155	Hydrazino dyethyl triazine
Ciba 16038	Aminoglutethimide
Cicrimina	Cycrimine
Cirpon	Meprobamate
Cirponyl	Meprobamate
Citrullamon	Phenytoin
Citrulliamon	Phenytoin
Comital	Phenytoin
Comitiadon	Phenacemide
Comitiona	Phenytoin
Compazine	Prochlorperazine
Contomin	Chlorpromazine
Contrazole	Zoxazolamine
Convexina	Trimethadoine
Convulsan	Mephenytoin
Covatine	Captodiame
Covatiz	Captodiame
Cyrpon	Meprobamate

D

Dadex	Dexamphetamine
D-Amfetasul	Dexamphetamine
Dapaz	Meprobamate
D.A.S.	Dexamphetamine
D-Ate	Dexamphetamine
D-Citramine	Dexamphetamine
Deaner	Deanol
Deflexol	Zoxazolamine
Denyl	Phenytoin
Dephadren	Dexamphetamine
Deprinol	Imipramine
Desoxyne	1. Dexamphetamine 2. Methamphetamine
Desoxypheno-barbitone	Primidone
Dexaline	Dexamphetamine
Dexalme	Dexamphetamine
Dexalone	Dexamphetamine
Dexamed	Dexamphetamine
Dexedrina	Dexamphetamine
Dexoval	1. Dexamphetamine 2. Methamphetamine
Dexsule	Dexamphetamine
Dexten	Dexamphetamine
Dextenal	Dexamphetamine
Dextro-Anfetamina	Dexamphetamine
Dextro-Profetamine	1. Amphetamine, 2. Dexamphetamine
Dextrosule	Dexamphetamine
Dezibarbitur	Phenobarbital
Diacarb	Acetazolamide
Diakarb	Acetazolamide
Diamox	Acetazolamide
Dianol	Deanol
Dienol	Deanol
Dietamine	Amphetamine
Difenin	Phenytoin
Difhydan	Phenytoin
Di-Hydan	Phenytoin
Dihydantoin	Phenytoin
Dilantin	Phenytoin
Dillantin	Phenytoin
Diluran	Acetazolamide
Dimapp	Promethazine
Dimethaen	Deanol
Dintoin	Phenytoin
Diocurb	Dexamphetamine
Diomax	Acetazolamide
Diphantoine	Phenytoin
Diphedal	Phenytoin
Diphedan	Phenytoin
Diphenin	Phenytoin
Diphentoin	Phenytoin
Diphenylan	Phenytoin
Diprazin	Promethazine
Diprozin	Promethazine
Direnil	Acetazolamide
Direx	Acetazolamide
Disipal	Orphenadrine
Diural	Acetazolamide
Diuretex	Acetazolamide
Diuribeta	Acetazolamide
Diuriwas	Acetazolamide
Diutazol	Acetazolamide
Diveron	Meprobamate
Domafate	Dexamphetamine
Dopamine	Amphetamine
Dormabrol	Meprobamate
Dormiral	Phenobarbital
Dormytal	1. Amobarbital, 2. Phenobarbital,
Dorsital	1. Pentobarbitall 2. Phenobarbita
Duneryl	Phenobarbital
Durophet	Amphetamine
Dynaphenyl	Dexamphetamine

E

Ecuanil	Meprobamate
Edemox	Acetazolamide
Edion	Trimethadione
Eferon	Phenacemide
Elastonin	Amphetamine
Elastonon	1. Amphetamine, 2. Dexamphetamine
Elipten	Aminoglutethimide
Eliranol	Promazine
Elyptene	Aminoglutethimide
Embutal	Pentobarbital
Emeside	Ethosuximide
Endiemal	Metharbital
Enphenemal	Methylphenobarbital
Epamin	Phenytoin
Epanal	Phenobarbital
Epanutin	Phenytoin
Epelin	Phenytoin
Ephadren	Dexamphetamine
Epiclase	Phenacemide
Epidion	Trimethadione
Epidorm	Phenobarbital
Epifenyl	Phenytoin

Epikur	Meprobamate
Epilan	1. Mephenytoin, 2. Phenytoin
Epilantin	Phenytoin
Epilunal	Mephenytoin
Epimid	Phensuximide
Epinat	Phenytoin
Epital	Mephenytoin
Eptal	Phenytoin
Eptoin	Phenytoin
Equanil	Meprobamate
Equatrate	Meprobamate
Equinil	Meprobamate
Equitar	Meprobamate
Eskabarb	Phenobarbital
Eskazine	Trifluoperazine
Esparin	Promazine
Esprivex	Triflupromazine
Etaminal	Pentobarbital
Ethaminal	Pentobarbital
Ethosuccinimide	Ethosuximide
Etilfen	Phebobarbital
Etroflex	Methocarbamol
Etydion	Trimethadione
Eumicton	Acetazolamide
Euneryl	Phenobarbital
Euphobine	Amphetamine
Euphodine	Amphetamine
Evrodex	Dexamphetamine

F

Fargan	Promethazine
Felsules	Chloral hydrate
Femiton	Methylphenobarbital
Fenacemid	Phenacemide
Fenacetil-Karbamid	Phenacemide
Fenamin	Amphetamine
Fenantoin	Phenytoin
Fenarol	Chlormezanone
Fenazil	Promethazine
Fenedrin	Amphetamine
Fenergan	Promethazine
Fenemal	Phenobarbital
Fenilep	Phenacemide
Fenitoina	Phenytoin
Fenobarbital	Phenobarbital
Fenobarbitalio	Phenobarbital
Fenobarbiton	Phenobarbital
Fenobarbitoon	Phenobarbital
Fenopromin	Amphetamine
Fenostenyl	Phenacemide
Fensuximide	Phensuximide
Fentoin	Phenytoin
Fenurone	Phenacemide
Fenytoine	Phenytoin
Flexin	Zoxazolamine
Flumazin	Triflupromazine
Flumezin	Fluphenazine
Fluomazina	Triflupromazine
Fluopromazine	Triflupromazine
Fluorofen	Triflupromazine
Fonurit	Acetazolamide

G

Gagexyl	Meprobamate
Gardenal	Phenobarbital
Gardepanyl	Phenobarbital
Gargenal	Phenobarbital
Geksamidin	Primidone
Gemonal	Metharbital
Gemonil	Metharbital
Gemonit	Metharbital
Gerol-Epilan	Mephenytoin
Gerot-Epilan-D	Phenytoin
Guiaphenesin Carbamate	Methocarbamol

H

Harmonin	Meprobamate
Hetamine	Dexamphetamine
Hexamidine	Primidone
Hexyphenidyl	Trihexyphenidyl
Hibanil	Chlorpromazine
Hiberna	Promethazine
Hibernal	Chlorpromazine
Hidantal	Phenytoin
Hidantina	Phenytoin
Holbamate	Meprobamate
Hydantal	Phenytoin
Hydantin	Phenytoin
Hydantoin	Phenytoin
Hydantoinal	Phenytoin
Hydral	Chloral hydrate
Hydrat Chloralu	Chloral hydrate
Hypnaletten	Phenobarbital
Hysteps	Phenobarbital

I

Ibiozedrine	Amphetamine
Idantoil	Phenytoin
Idantoin	Phenytoin
Idrossizina	Hydroxyzine
Imizin	Imipramine
Insulton	Mephenytoin
Isamin	Amphetamine
Isoamyne	Amphetamine
Isobarb	Pentobarbital
Isoethadione	Paramethadione
Isomyn	Amphetamine
Isomytal	Amobarbital
Isonal	1. Amobarbital, 2. Aprobarbital, 3. Methylphenobarbital
Isophenergan	Promethazine
Isopromethazine	Promethazine
Iturate	Pentobarbital

J

Jatroneural	Trifluoperazine

K

Kemadrin	Procyclidine
Khloralgidrat	Chloral hydrate
Klopromex	Chlorpromazine

L

Largactil	Chlorpromazine
Largaktil	Chlorpromazine
Largaktyl	Chlorpromazine

Ledamox	Acetazolamide
Lemazina	Promazine
Lentanet	Dexamphetamine
Leodrin	Amphetamine
Leonal	Phenobarbital
Lepinal	Phenobarbital
Lepitoin	Phenytoin
Lergigan	Promethazine
Levonor	Amphetamine
Librium	Chlordiazepoxide
Lifene	Phensuximide
Linampheta	Amphetamine
Linasen	Phenobarbital
Linaxar	Styramate
Liquital	Phenobarbital
Liranol	Promazine
Listica	Hydroxyphenamate
Lixophen	Phenobarbital
Lorinal	Chloral hydrate
Luminal	Phenobarbital
Lycoral	Chloral hydrate
Lyogen	Fluphenazine

M

Madiol	Meprobamate
Mallorol	Thioridazine
Malloryl	Thioridazine
Margonil	Meprobamate
Masmoran	Hydroxyzine
Maxiton	Dexamphetamine
Mebaral	Methylphenobarbital
Mebarol	Methylphenobarbital
Mebubarbital	Pentobarbital
Mebumal	Pentobarbital
Mechloral	Chloral hydrate
Mecodrin	Amphetamine
Medianox	Chloral hydrate
Mefenal	Methylphenobarbital
Mefenalettae	Methylphenobarbital
Mefenamina	Orphenadrine
Mefobarbital	Methylphenobarbital
Megaphen	Chlorpromazine
Meleril	Thioridazine
Mellaril	Thioridazine
Mellerettes	Thioridazine
Melleril	Thioridazine
Mepantin	Meprobamate
Mepavlon	Meprobamate
Mephenamin	Orphenadrine
Mephenetoin	Mephenytoin
Mephobarbital	Methylphenobarbital
Mepranil	Meprobamate
Meprin	Meprobamate
Meprobam	Meprobamate
Meproban	Meprobamate
Meprodil	Meprobamate
Meprosin	Meprobamate
Meprospan	Meprobamate
Meprotabs	Meprobamate
Meprotan	Meprobamate
Meprozine	Meprobamate
Mesantoin	Mephenytoin
Mesontoin	Mephenytoin
Metabarbital	Metharbital
Metaminodiazepossido	Chlordiazepoxide
Metanin	Procyclidine
Methabarbital	Methabarbital
Methaminodiazepoxide	Chlordiazepoxide
Methantoin	Mephenytoin
Methoin	Mephenytoin
Methylnirvanol	Mephenytoin
Methylphenetoin	Mephenytoin
Metocarbamol	Methocarbamol
Metydan	Mephenytoin
Milontin	Phensuximide
Milonton	Phensuximide
Miltamato	Meprobamate
Miltaun	Meprobamate
Miltown	Meprobamate
Minetoin	Phenytoin
Minoaleviatin	Trimethadoine
Miotran	Chloroxazone
Miowas	Methocarbamol
Moditen	Fluphenazine
Molinal	Phenobarbital
Monetamine	Amphetamine
Monophos	Amphetamine
Morbam	Meprobamate
Muskel	Chlormezanone
Mylepsin	Primidone
Myophane	Orphenadrine
Mysoline	Primidone

N

Napental	Pentobarbital
Natrionex	Acetazolamide
Nembutal	Pentobarbital
Neoflex	Chlorzoxazone
Neo-Hibernex	Promazine
Neophedan	Phenacemide
Neos-Hidantoina	Phenytoin
Neo-Tran	Meprobamate
Nervonus	Meprobamate
Neuraxin	Methocarbamol
Neurobarb	Phenobarbital
Neuropromazin	Chlorpromazine
Neurosene	Sodium bromide
Nevrotamine 4	Phenobarbital
Nipodal	Prochlorperazine
Nirvanol	Ethotoin
Nirvanal	Phenobarbital
Noctec	Chloral hydrate
Noptial	Phenobarbital
Norephedrane	Amphetamine
Norflex	Orphenadrine
Novamin	1. Dimenhydrinate 2. Diphenhydramine 3.Prochlorperazine
Novomazina	Chlorpromazine
Numol	Phenobarbital
Nuncital	Emylcamate
Nunol	Phenobarbital

O

Oasil	Meprobamate
Obesedrin	Dexamphetamine
Obesonil	Dexamphetamine
Odemin	Acetazolamide
Omca	Fluphenazine
Om-Hydantoine	Phenytoin
Opromazin	Chlorpromazine
Orolevol	Meprobamate
Orphenadril	Orphenadrine

Ortedrine	Amphetamine
Orthedrin	Amphetamine
Oxylan	Phenytoin

P

Pabenol	Deanol
Pacinol	Fluphenazine
Pacitane	Trihexyphenidyl
Pagitane	Cycrimine
Palapent	Pentobarbital
Panbule	Pentobarbital
Panediol	Meprobamate
Pan-Tranquil	Meprobamate
Paradione	Paramethadione
Paraflex	Chlorzoxazone
Paralest	Trihexyphenidyl
Parekin	Orphenadrine
Pargitan	Trihexyphenidyl
Parkinsan	Trihexyphenidyl
Partigan	Trihexyphenidyl
Paxin	Meprobamate
Peganone	Ethotoin
Pellcaps	Dexamphetamine
Pembules	Pentobarbital
Pentale	Pentobarbital
Pentobarbitone	Pentobarbital
Pentobrocanol	Pentobarbital
Pento-Del	Pentobarbital
Pentone	Pentobarbital
Pentyl	Pentobarbital
Peragit	Trihexyphenidyl
Perequil	Meprobamate
Permitil	Fluphenazine
Perquietil	Meprobamate
Pertranquil	Meprobamate
Petidion	1. Ethadione 2. Trimethadione
Petidon	Trimethadione
Petilep	Trimethadione
Petimalin	Trimethadione
Petnidan	Ethosuximide
Phacetur	Phenacemide
Phaldrone	Chloral hydrate
Phanantine	Phenytoin
Pharmamedrine	Amphetamine
Phasein	Orphenadrine
Phemitone	Methylphenobarbital
Phenacereum	Phenacemide
Phenacetur	Phenacemide
Phenaemal	Phenobarbital
Phenalum	Phenacemide
Phenamine	Amphetamine
Phenatoin	1. Mephenytoin, 2. Phenytoin
Phenedrine	Amphetamine
Phenemal	Phenobarbital
Phenergan	Promethazine
Phenicarb	Phenacemide
Phenobal	Phenobarbital
Phenobarbitone	Phenobarbital
Phenobarbyl	Phenobarbital
Phenonyl	Phenobarbital
Phenoturic	Phenobarbital
Phenpromin	1. Amphetamine 2. Dexamphetamine
Phenurone	Phenacemide
Phenutal	Phenacemide
Phenylbarbital	Phenobarbital
Phenyrit	Phenacemide
Phetadex	Dexamphetamine
Phetylureum	Phenacemide
Phob	Phenobarbital
Pipanol	Trihexyphenidyl
Pipolphen	Promethazine
Placidol	Hydroxyzine
Placidon	Meprobamate
Prazine	Promazine
Prenderol	Diethylpropanediol
Prendiol	Diethylpropanediol
Prequil	Meprobamate
Primaclone	Primidone
Proazamine	Promethazine
Probamato	Meprobamate
Probamyl	Meprobamate
Procalmadiol	Meprobamate
Procalmidol	Meprobamate
Procarbamide	Meprobamate
Prochlorpemazine	Prochlorperazine
Procit	Promethazine
Proclopromazina	Prochlorperazine
Profamina	Amphetamine
Profetamine	Amphetamine
Prolamine	Methylphenobarbital
Prolixin	Fluphenazine
Promacina	Promazine
Promactil	Chlorpromazine
Promanyl	Promazine
Promazil	Chlorpromazine
Promazinamid	Promethazine
Promazionon	Promazine
Promezathine	Promethazine
Promiben	Imipramine
Prominal	Methylphenobarbital
Promitone	Methylphenobarbital
Promwill	Promazine
Propaphenin	Chlorpromazine
Propazin	Promazine
Propisamine	Amphetamine
Proptane	Dexamphetamine
Proquanil	Meprobamate
Protactyl	Promazine
Protazine	Promethazine
Prothazin	Promethazine
Pro-Tran	Promazine
Prozil	Chlorpromazine
Psychedrine	Amphetamine
Psychedryna	Amphetamine
Psychoton	Amphetamine
Psyquil	Trifluprom azine
Ptimal	Trimethadione
Pyrethia	Promethazine

Q

Quaname	Meprobamate
Quanil	Meprobamate
Quilaflex	Methaminonenzo-dioxan

R

Racephen	Amphetamine
Raphetamine	Amphetamine
Recrein	Deanol

Rectules	Chloral hydrate
Rela	Carisoprodol
Relberan	Chlordiazepoxide
Reostral	Meprobamate
Repocal	Pentobarbital
Restenil	Meprobamate
Restinal	Meprobamate
Restinil	Meprobamate
Revidex	Dexamphetamine
Rilaquil	Chlormezanone
Robaxin	Methocarbamol
Robaxon	Methocarbamol

S

Sacerno	Mephenytoin
Sagatal	Pentobarbital
Sanoma	Carisoprodol
Sedantoin	Mephenytoin
Sedantoinal	Mephenytoin
Sedanyl	Meprobamate
Seda-Ped	Phenobarbital
Sedazil	Meprobamate
Sediston	Promazine
Sedobromal	Sodium bromide
Sedocentillen	Phenobarbital
Seren Vita	Chlordiazepoxide
Setran	Meprobamate
Sevenal	Phenobarbital
Sevinol	Fluphenazine
Shalvaton	Meprobamate
Silantin	Phenytoin
Simpamina	Amphetamine
Simpamina-D	Dextroamphetamine
Simpatedrin	Amphetamine
Sinaxar	Styramate
Siqualine	Fluphenazine
Siquil	Triflupromazine
Sodantoin	Phenytoin
Sodanton	Phenytoin
Sodico-W	Phenobarbital
Solantin	Phenytoin
Solantoin	Phenytoin
Solantyl	Phenytoin
Solaxin	Chlorzoxazone
Soma	Carisoprodol
Somadril	Carisoprodol
Somalgit	Carisoprodol
Somanil	Carisoprodol
Sombutal	Pentobarbital
Somnolens	Phenobarbital
Somnoletten	Phenobarbital
Somnos	Chloral hydrate
Somnosan	Phenobarbital
Somonal	Phenobarbital
Sonia	Chlordiazepoxide
Sontec	Chloral hydrate
Sopental	Pentobarbital
Sorosil	Chloral hydrate
Sotyl	Pentobarbital
Sowell	Meprobamate
Sparine	Promazine
Spasepiletten	Phenobarbital
Spasepilin	Phenobarbital
Starazine	Promazine
Starifen	Phenobarbital
Starilettae	Phenobarbital
Stelazine	Trifluoperazine
Stementil	Prochlorperazine
Stemetil	Prochlorperazine
Stental	Phenobarbital
Stimulan	Amphetamine
Striatran	Emylcamate
Succitimal	Phensuximide
Surplix	Imipramine
Suvren	Captodiame
Suxinutin	Ethosuximide
Sympametin	Amphetamine
Sympamine	1. Amphetamine, 2. Dexamphetamine
Sympatedrine	Amphetamine
Synatan	Dexamphetamine

T

Tacosal	Phenytoin
Talofen	Promazine
Tanidil	Promethazine
Tanphetamine	Dexamphetamine
Temaril	Alimemazine
Tementil	Prochlorperazine
Tempodex	Dexamphetamine
Tensofin	Fluphenazine
Tensol	Meprobamate
Tensonal	Meprobamate
Teolaxin	Phenobarbital
Terfluzin	Trifluoperazine
Thiergan	Promethazine
Thorazene	Chlorpromazine
Thorazine	Chlorpromazine
Tigloidine	Tropigline
Tiglyl Tropine	Tropigline
Tofranil	Imipramine
Toin	Phenytoin
Torazina	Chlorpromazine
Trancin	Fluphenazine
Trancopal	Chlormezanone
Tran-Q	Hydroxyzine
Tranquil	Meprobamate
Tranquiline	Meprobamate
Tranquisan	1. Meprobamate, 2. Perphenazine
Trelmar	Meprobamate
Tresortil	Methocarbamol
Trianton	Mephenytoin
Tridilona	Trimethadione
Tridione	Trimethadione
Triexifenidila	Trihexyphenidyl
Trilidona	Trimethadione
Trimedal	Trimethadione
Trimedone	Trimethadione
Trimetadione	Trimethadione
Trimetin	Trimethadione
Trioxanona	1. Phenacemide 2. Trimethadione
Triozanona	Trimethadione
Triphenidyl	Trihexyphenidyl
Tropine Tiglate	Tropigline
Troxidone	Trimethadione

U

Urbil	Meprobamate

V

Vagosin	Procyclidine
Valium	Diazepam
Vallergin	Promethazine
Verophen	Phenobarbital
Vespazine	Fluphenazine
Vespral	Triflupromazine
Vesprin	Triflupromazine

W

Wintermin	Chlorpromazine
Wodan Chloralu	Chloral hydrate
Wodnik Chloralu	Chloral hydrate
Wodzian Chloralu	Chloral hydrate

Z

Zamine	Dexamphetamine
Zarontin	Ethosuximide
Zentropil	Phenytoin
Zoxamin	Zoxazolamine