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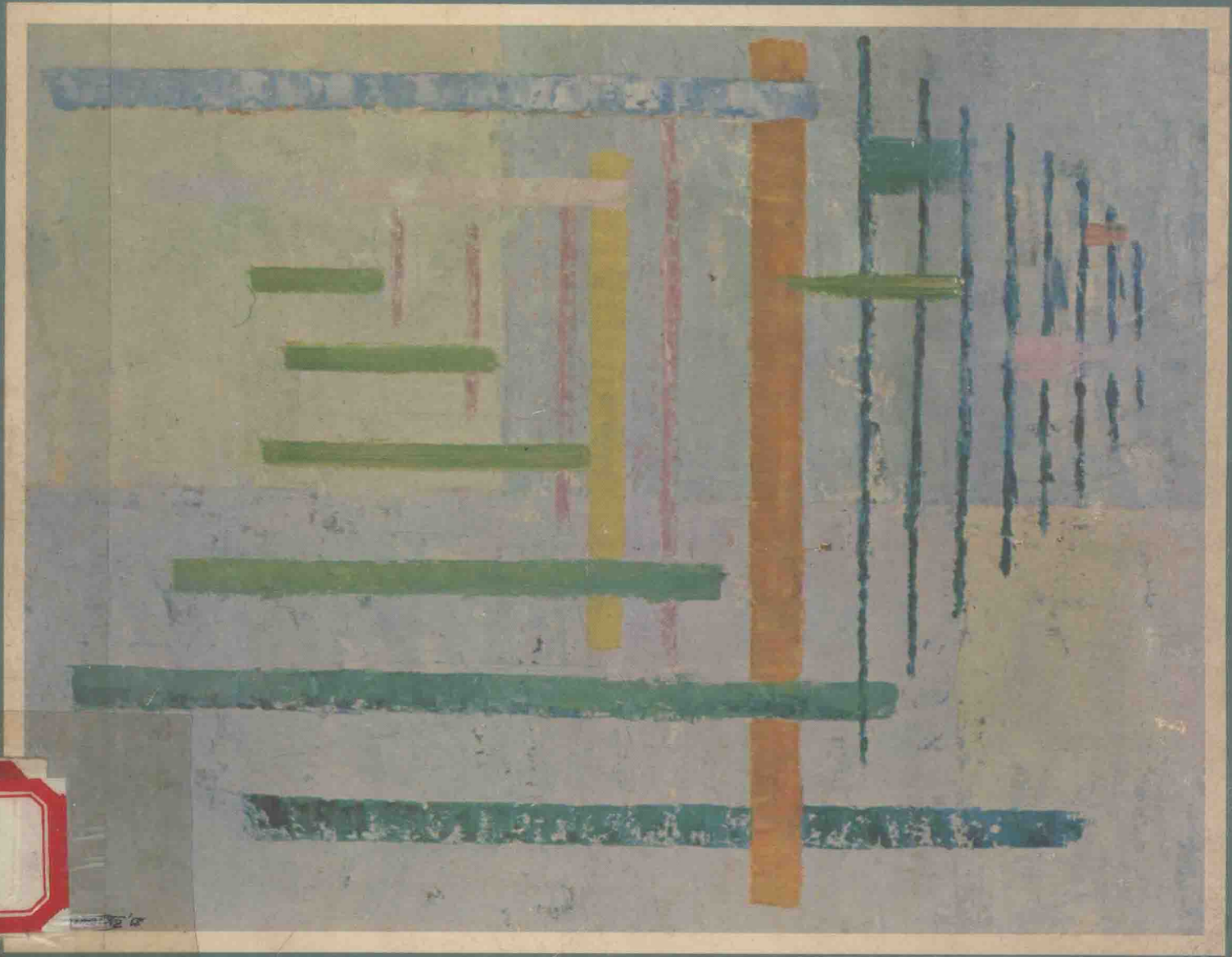
The Broad Range of Use of Diphenylhydantoin

BIBLIOGRAPHY AND REVIEW



THE DREYFUS MEDICAL FOUNDATION

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The Broad Range of Use of Diphenylhydantoin

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THE DREYFUS MEDICAL FOUNDATION

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Many physicians and scientists have
made invaluable contributions to this field.
To them we express our admiration.

To our friends and colleagues
who have helped us so much,
we express our deepest appreciation.
In particular, we would like to thank
Dr. William J. Turner.

Perspective

Diphenylhydantoin (DPH) has been a well known medicine for over thirty years.* During most of this time it has been classified as an anticonvulsant. This classification has been unfortunate, not because it is inaccurate but because it has implied that DPH is limited to its anticonvulsant properties.

We now know that DPH is a substance with broad therapeutic effectiveness. For a perspective we suggest that the reader turn to page 61 and look at the extensive list of Symptoms and Disorders for which DPH effectiveness has been reported.

If one wonders how the general use of DPH could have been overlooked for so long, a review of its history may help. The first benefits of DPH were discovered by Putnam and Merritt in 1937. They were looking for a medicine to help the epileptic and they found one. It is a rare feat to find what one seeks in medical research. We now know that the discovery was even more remarkable than that which was sought. Putnam and Merritt in their earliest paper pointed towards broader implications when they observed ". . . it was frequently noted by the parents of children (that took DPH) that they were much better behaved, more amenable to discipline and did better work in school."

Since Putnam and Merritt were looking specifically for an anticonvulsant, it is understandable that DPH was quickly labeled an anticonvulsant or antiepileptic. As has been mentioned earlier, this limiting classification tended to obscure the general value of DPH.

In 1885 Gowers observed that "Of all the immediate causes of epilepsy the most potent are psychical—fright, excitement, anxiety." This brings into focus the fact that the medicines that preceded DPH in the treatment of epilepsy, first the bromides and second phenobarbital, were not specifics for epilepsy but were medicines with broad use in the nervous system. It is therefore not surprising that DPH also has broad use in the

*A number of companies manufacture diphenylhydantoin. Since patents expired some years ago its manufacture is not restricted.

nervous system—and it should be noted that unlike its predecessors DPH is not a sedative and it is not addictive.

Putnam and Merritt established the effectiveness of DPH by giving it to cats in which convulsions were electrically induced. DPH modified or controlled these convulsions. It also modified or controlled the convulsions of the epileptic. It could have been deduced at that time that DPH had a modifying or regulating effect on electrical activity.* External electrical activity caused the convulsions in the cats. Internal (bio) electrical activity is involved in the convulsions of the epileptic.

When DPH is viewed as a substance that has a regulating effect on bioelectrical activity, the breadth of its potential becomes apparent. Bioelectrical activity is a property common to all live cells. In fact, one definition of a dead cell is a cell that has no bioelectrical activity. The rhythms of the heart are electrically regulated, and the rhythms of the digestive tract are electrically influenced. Messages of pain are electrically transmitted and stimuli for anger and fear are electrically relayed. With an estimated ten billion interconnected nerve cells there is a high concentration of bioelectrical activity in the brain. Therefore it is easy to understand that a medicine which regulates or modifies bioelectrical activity can be effective in a wide variety of medical disorders.

The purpose of this bibliography is to put together in one place much of the work that has been done on the clinical uses of DPH, and on its basic mechanisms of action. When the many facets of this medicine are viewed as a whole, a new perspective of DPH emerges.

*This deduction would have proved correct. See studies on regulation of post-tetanic potentiation and stabilization of excitable membranes under Basic Mechanisms of Action.

Summary of Basic Mechanisms

Diphenylhydantoin (DPH) has a stabilizing effect on the excitability of individual nerve cells and nerve tissue. This effect is reported in peripheral nerve, in spinal cord, in neuromuscular junction and in brain. In addition, DPH is reported to stabilize excitable membrane in skeletal muscle, smooth muscle and cardiac muscle. DPH counteracts hyperexcitability in nerve induced by lowered calcium concentration. DPH decreases or eliminates post-tetanic potentiation, an increase in neuronal excitability following rapid repetitive electrical presynaptic stimulation. DPH in proper amounts does not impair the ability of nerve fibers to carry impulses at high frequency; nor does it notably alter normal excitation and response properties of neurons. DPH has been studied in both vertebrates and invertebrates.

When intracellular sodium is abnormally high or intracellular potassium is abnormally low, DPH is reported to act in the direction of correcting this imbalance; and when sodium or potassium are in the normal range, DPH either leaves these concentrations essentially unchanged or effects minimal decreases in intracellular sodium. DPH acts to stabilize blood sugar levels in labile diabetes. It is reported to combat anoxia and to increase energy reserve compounds in brain, namely, glucose, glycogen, ATP, and creatine phosphate. Taken together these basic mechanism findings are consistent with clinical findings that have caused DPH to be referred to as a stabilizer, a regularizer, or a normalizer.

Although DPH is observed to have a beneficial effect on pain and sleep disturbances, it is reported not to diminish impulse transmission through the ascending reticular formation. DPH is reported to counteract the toxic effects of digitalis without impairing inotropic benefits. Individuals who have taken DPH for more than three months were found to have significantly lower blood levels of DDE, the principal metabolite of DDT. DPH has been reported to reduce the incidence and severity of convulsive activity due to acute radiation exposure.

Other reported effects of DPH include increase in the flow of blood in coronary and cerebral blood vessels, regulatory effects on ACTH and cortisone secretion, decrease of dermal lipids, decrease of brain acetylcholine, and increase in brain gamma aminobutyric acid (GABA).

Summary of Clinical Uses

DPH has been found useful in the treatment and prevention of a wide range of disorders. Among them are cardiac arrhythmias, neuromuscular disorders, sleep disturbances, migraine and other headaches, and neuralgias. For a more complete listing see Clinical Uses, page 17.

In this summary only one area of the therapeutic use of DPH will be discussed—that is the important and central use of DPH in thought, mood and behavior disorders.

DPH has a therapeutic effect on the overactive brain. Symptoms of this condition are preoccupation, multiple thinking, and flashes and fragments of thoughts coming and going. DPH reduces this uncontrolled activity enabling more normal thinking processes to be restored. This effect is usually achieved within an hour. The therapeutic effect that DPH has on the overactive brain is consistent with basic mechanism findings that DPH decreases hyperexcitability in brain cells.

Anger and fear and related emotions are usually found in combination with the overactive brain. Emotional states related to anger for which DPH is therapeutic are impatience, impulsiveness, irritability, aggression, hostility, rage and violence. Emotional states related to fear for which DPH is therapeutic are worry, anxiety, guilt, pessimism and depression. Although excessive anger and excessive fear are decreased or eliminated by DPH, realistic reactions of anger and fear are not interfered with.

Sleep disturbances found in combination with the overactive brain fall into two general categories. The first and most frequent category is symptomatized by difficulty in falling asleep because of overthinking, light sleep accompanied by unpleasant dreams and frequent nightmares, and insufficient sleep. A second category is symptomatized by excessive sleep, so-called avoidance sleep. Relief from both types of sleep disturbance is usually prompt with DPH.

DPH is effective with extremes of mood ranging from depression to the hyperexcitable state. These apparent disparate effects are observed in the overactive irritable individual who is calmed by DPH and the tired energyless individual who has a return to normal energy levels.*

Somatic symptoms associated with thought, mood and behavior dis-

*This clinical effect is supported by basic mechanism studies that indicate that DPH tends to increase brain levels of glucose, glycogen, ATP and creatine phosphate, and that it combats anoxia.

orders are usually relieved by DPH. Among those most frequently observed are headaches, gastrointestinal disorders, pain in back of neck and other pain, shortness of breath, trembling, muscle spasms, skin disorders, and problems with weight. DPH has been found effective in the treatment of acute alcoholism and in the prevention of alcoholism.

DPH is not reported to conflict with commonly used sedatives, tranquilizers or energizers. Alcohol and DPH are not incompatible.* It is well recognized that DPH is not a sedative and it is not habit-forming.

The range of safety of DPH has been established by over thirty years of extensive use.

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*This compatibility with alcohol should not be confused with the fact that in epilepsy alcohol is contraindicated.

Discussion

The clinical observations of the use of DPH are consistent with the basic mechanisms of action of DPH which demonstrate that it has a regulatory effect on bioelectrical activity and stabilizes excitable nerve cell and nerve tissue. It is recognized that problems of the nervous system are associated with a wide variety of medical disorders. If one thinks of the common denominator of these disorders as a problem of bioelectrical activity, then grand mal epilepsy can be viewed as an extreme manifestation of this type of problem. There are many stages and conditions of above-normal excitability of nerve cells which do not result in grand mal epilepsy. Some of these are reflected in abnormal electroencephalograms, but many more are not and are seen as behavioral indications of hyperexcitability such as impatience, irritability, impulsiveness and excessive anger, as well as worry, anxiety, fear and depression.

Perhaps thirty-three years ago when the first benefits of DPH were discovered, the thought that bioelectrical activity in the nervous system would have a basic relationship to anger and fear would not have been met with wide acceptance. Today, because of the work of Hess, Penfield, Delgado and others a relationship between electrical stimulation and anger and fear has been demonstrated. Thus, it is far easier today to

understand that excessive bioelectrical activity can be the source of excessive anger and fear; and that a substance that tends to stabilize bioelectrical activity can have a beneficial effect against anger and fear. Regardless of mechanism, clinical studies clearly demonstrate that DPH has a therapeutic effect on excessive anger and fear.*

If, as it appears, DPH's clinical effectiveness is related to the regulation of bioelectrical mechanisms, since every living cell is invested with bioelectrical activity, then all of the therapeutic uses of DPH have not yet been explored.

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*When one considers the role that excessive anger and fear play in violence and addiction one realizes that one of the important uses of DPH may be as a preventive against addiction and violent behavior. In addition to the sociological problems involved, violence and addiction are disorders that need medical attention. Because DPH is non-addictive, is not a sedative, and has a wide range of safety, it is particularly well suited for this purpose. (See DPH as a Preventive, pages 54-55, and Surgery, page 52.)

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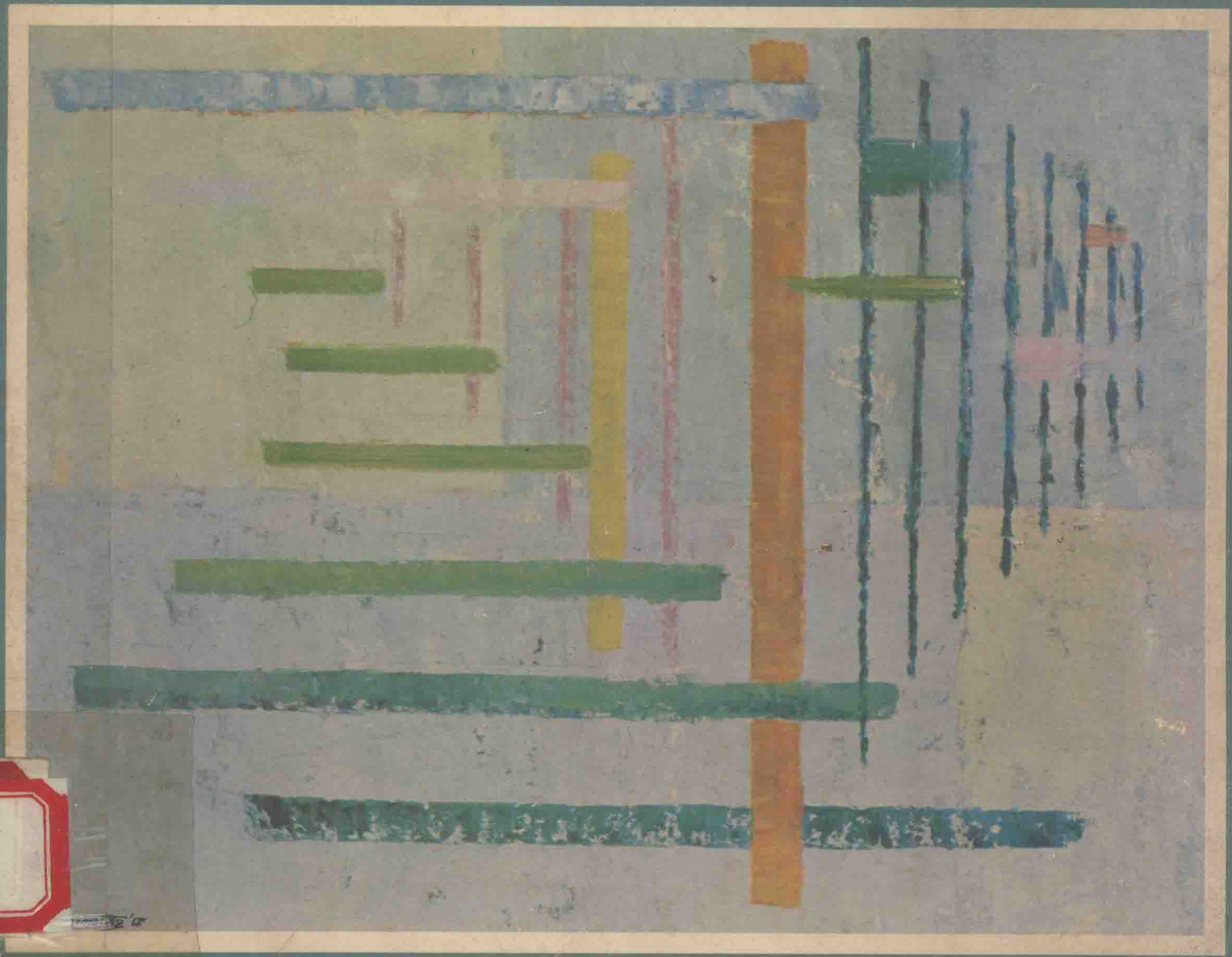

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