NEWER DRUGS WHICH INFLUENCE BEHAVIOR

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Many chemicals affect the behavior of children in health and in disease. Often the precise mode of action of these is elusive. The effect of insulin in erasing coma from a diabetic child is better known to us than the method by which the insulin does so. When a chemical has a reproducible effect—either preventive or therapeutic—which is considered desirable, we use it. The therapeutic skeptic merely wants to know that an agent will have a regular reproducible effect not otherwise to be expected. The therapeutic cynic however refuses to accept demonstrated facts if he cannot personally fathom the modus operandi. Fortunately, there remain workers who pursue successes with productive discontent until they learn how and why various agents work, how to improve them, and what the immediate and long-term consequences may be for an individual or for the group receiving them.

Chemotherapy for behavior disorders poses many questions, which may go beyond what is often considered the province of medicine. Yet, responsibilities of physicians seem to be growing broader. It is apparent that the administration of chemicals which may influence personal behavior carries large moral, ethical and social considerations. This is particularly true in pediatrics because our patients are on that rapidly moving platform termed growth and development. The very possibility of chemically modifying habits, values, social adaptation and even the learning process itself is an awesome prospect.

It has been said that modern pediatrics deals with three major related areas—which in order of seniority of conquest are Nutrition, Infection, and Behavior. Problems remain and will continue in all three areas, although surely it is clear that giant strides have been taken in the first two areas. Perhaps lessons may be learned and solace found in reflecting upon the fact that we did not always do as well or as simply by our children in the areas of applied nutrition and the infectious disorders as now. The slide rule and scale for formula preparation, the mustard plaster and turpentine stupe for pneumonia have been more or less reverently laid aside. The introduction of methods of precision and of preventive and therapeutic specifics in nutrition and in the field of infectious diseases arose through intensive clinical and laboratory research fired by a dissatisfaction with the status quo.

For a long time the pediatrician’s efforts in the three major areas were restricted to the rules of hygiene. Specifics strengthened the position without displacing hygiene in the nutritional and infectious disease spheres. In its evolution, may we not hope for specifics to strengthen mental hygiene?

Methods of precision and chemical and surgical specifics in the behavioral field are in their infancy and it is to be hoped that they will grow lustily. What are the grounds for these hopes?

CHEMICAL CONSIDERATIONS

Induction and Reversal of Mental Aberration

LSD-25 (d-lysergic acid diethylamide), a semi-synthetic ergot derivative, in low oral dosage of 1 to 2 mg/kg of body weight, produces various psychotic reactions. The psychotic effects of this ergot derivative bring to mind the fact that outbreaks of psychopathic behavior have been described for centuries in various parts of Europe when ergot-infested grain was consumed. LSD-25 has been used more recently to study induced mental disturbances in fish. Further-
more, mescaline, an alkaloidal derivative of cactus plants and yohimbine have been used in various tribal rites to transform the human mind.

The effects of such preparations have been studied closely in human volunteers. Anxiety, mania, euphoria, depression, withdrawal, apathy, suspicion, uncontrollable crying or giggling, illusions and hallucinations may occur singly and together.

Although differing widely chemically (Fig. 1), these preparations have a common indole nucleus and a substituted amino-ethyl side chain. Studying guppies made insane by LSD-25, it was found that pre-treatment with indole enhanced the LSD-25 effect. The indole nucleus is believed by some investigators to hold an important clue to normal and abnormal mentation. Thus, serotonin which has been studied in hypertensive states influenced by reserpine, is an indole derivative and a natural constituent of the brain.

Of great importance is the fact that chemically induced mental aberration can be reversed. For example after the ingestion of LSD-25 and mescaline by physicians serving as volunteer subjects, the psychotic behavior induced was abruptly terminated by the injection of chlorpromazine.  

**Chemically Induced Serenity**

Twenty-five years ago in his fable *Brave New World*, Aldous Huxley described the effects of Soma, his fictitious synthetic chemical for transforming the mind into a happy, accepting state without impairment of usefulness. Laboratory observation of the past few years has suggested that a variety of animals may be made serene chemically by at least three types of drugs: phenothiazine derivatives, reserpine, and meprobamate. Even the lowly spider has his drive but not his craftsmanship curtailed by chlorpromazine. So reports one investigator who placed this potion in the spiders’ water whereupon they produced fewer but technically normal webs. Inherently hostile monkeys are made docile and the Siamese fighting fish is said to abandon its inborn pugnacity in the presence of chlorpromazine, reserpine or meprobamate. The prospects are invitingly awesome.

Before taking up the three groups of chemicals most actively under consideration in behavioral chemotherapy, it is pertinent to comment briefly upon certain neuro-anatomical considerations.

The site of action of these groups of chemicals is at a level below the cortex. It may seem specious or irreverent to some to speak of the neuroanatomy of emotion. Papez, summarizing the data and proposing a hypothesis in 1937 asked, “Is emotion a magic product, or is it a physiologic process which depends on an anatomic mechanism?” His report includes much information relative to structural units of the rhin-
encephalon—the nose brain which in lower animals determines their fight or flight responses. Extensive work by Magoun7 and the interesting psychosurgical, experimental work of Heath's group of psychiatrists in these areas of the intact brain are gradually lifting the fog which enshrouds the mediative mechanisms of emotion.

THE THREE MAJOR GROUPS OF NEWER DRUGS

Phenothiazine Derivatives

The two chief forms (Fig. 2) are chlorpromazine hydrochloride (available as Thorazine®) and promazine hydrochloride (available as Sparine® and as Compazine®). These drugs were prepared originally in France in the synthesis of various antihistaminics, the mode of action of which is likewise not clear. It is believed that the phenothiazine derivatives act upon the higher centers in the diencephalon by inhibiting certain chemoreceptor zones in the hypothalamus and reticular substance.

From the standpoint of behavior the more outwardly disturbed the child, the more effective has been chlorpromazine, whether the emotional problem occurs alone or in combination with organic disease. Thus as assaultive, destructive, hyperkinetic, inattentive children have been made tractable with reasonable success. The drug has thus been helpful in the management of severely disturbed children committed to institutions.8, 10 Similar results have been achieved with severely antisocial children living outside institutions.11 Individual variation in dosage may be extremely important. A revealing example of this from the practice of a neighboring pediatric colleague follows:

D.W., a 9-year-old, inattentive, destructive boy who when dealt with for such things as setting fires or smashing property would soon repeat such acts; he "could not learn right from wrong." Competent neurologic and psychotherapeutic assistance yielded imperceptible change in his behavior. Chlorpromazine was prescribed; 10 days later the mother reported striking improvement in behavior but complained of the high cost of the prescription. Investigation revealed that 100 mg four times daily had been dispensed when a 10 mg dose was intended. To avoid concern, the change to the intended 40 mg daily was made unobtrusively. At the end of another 10 days the frustrated mother stated that the medication no longer was effective. Upon unobtrusive return to the daily dosage of 400 mg, tractable behavior ensued. This is perhaps an unusual instance of the importance of individualizing dosage.

Milder behavioral habit disturbances such as nail biting, temper tantrums, habit tics and enuresis are not as frequently corrected, unless they are concomitant parts of the picture in a more seriously disturbed child.

![Fig. 2. Note the structural similarity of promazine and chlorpromazine to the "antihistaminic" Phenergan.](http://pediatrics.aappublications.org/)

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The side reactions personally observed with chlorpromazine have been drowsiness, abdominal distension and mild hypotension when used parenterally in children for purposes other than modification of behavior.\textsuperscript{12} In adults, intrahepatic obstructive jaundice, agranulocytosis, skin reactions and parkinsonian tremors have been observed on occasion.

The other phenothiazine derivative, promazine, has been used too short a time in children for personal comment. It may be hoped it will have all of the advantages of its analogue chlorpromazine, with fewer side reactions in view of the smaller doses recommended.

**Reserpine**

Reserpine is a recently isolated active alkaloid of the Rauwolfia serpentina shrub which in turn has been used by Asiatic herb doctors for centuries in various central nervous system derangements. Reserpine itself was introduced in America primarily in the management of hypertension in adults. Its non-hypnotic effect on tension and anxiety were interesting properties which led quickly to a variety of clinical trials on behavior.\textsuperscript{13}

One's reaction from anecdotal research with colleagues and personal experience is that the frequency of nasal congestion as an undesirable side effect in small children interferes with its prolonged use. Nevertheless, it may be useful in interrupting a series of undesirable behavioral circumstances and habits. Among infants, these include the colicky, fussy, irregularly sleeping young infant, the true ruminator, and those with head banging, head nodding and rolling, and body rocking. Similarly, older children who are fidgety with or without nail biting, nocturnal teeth grinding, and night terrors have responded not infrequently. Some children with cerebral palsy have been sufficiently quieted under reserpine's influence as to be more accessible for therapy.

**Meprobamate**

This is available as Equanil\textsuperscript{\textregistered} and Miltrin\textsuperscript{\textregistered}. This drug is a chemical derivative of the muscle relaxant, mephenesin (Tolserol\textsuperscript{\textregistered}) and is believed to block abnormal stimuli in various inter-neuronal circuits in the thalamus. Its chemical structure is simpler (Fig. 3) than the other so-called tranquilizers mentioned, lacking ring structures or unsaturated linkages.\textsuperscript{14} Theoretically this should mean less risk of toxicity. It is doubtful whether this latter point has influenced the stars of stage, screen and radio and others who have affectionately acclaimed its jolly effects.

As yet, meprobamate appears to have been used less than the other tranquilizers in general pediatrics. However, in cerebral palsy, its effects have been promising in some children with predominantly tension athetosis. It is too early to predict its place in the growing number of mental medications.

Fortunately there have been few incestuous pharmaceutical unions between these different groups of agents. More and more

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\text{NH}_2 &- \text{CO} - \text{O} - \text{CH}_2 - \text{C} - \text{CH}_2 &- \text{O} - \text{CO} - \text{NH}_2 \\
\text{CH}_2 &- \text{CH}_2 &- \text{CH}_3
\end{align*}
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**M E P R O B A M A T E**

Fig. 3. Note absence of ring structures and of unsaturated linkages which should theoretically diminish toxic reactions.
medicinal matrimony (Fig. 4) has become the manufacturer's mode in general. It is hoped that we shall be enabled to select ingredients by individual dosage rather than be overwhelmed by premixed cocktails with alluring trademarks.

**SUMMARY**

It has been pointed out that certain chemically related compounds can induce mental aberration in man and animals which other chemicals can correct. These latter chemicals are capable of modifying the inherent aggression of certain lower animals and of inducing serenity in some humans with disturbances of mentation and behavior. The duration of effects, the long-range consequences, the possibility of habituation remain important unknowns.

Comparisons have been drawn among the three large areas of pediatric interest—Nutrition, Infection, Behavior. These have been dominated in a natural evolutionary sequence by the applied rules of hygiene until such time as precise methods and potent specifics were available. The dawn of these methods in the field of Behavior may be at hand. It is unnecessary to point out the fantastic importance of scientific study of behavior, particularly in children whose habits and human values are being shaped by the learning process. The orthodox, conservative, methodical, dispassionate methods of medical research, combining the talents of clinical and basic science, have brought rich rewards to children in the areas of Nutrition and Infection. There is hope that this same approach, if untrammeled by the fanfare of hucksterism—medical or lay, will sometime in the future bring important rewards in the area of Behavior.

**REFERENCES**

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*Pediatrics* 1957;20;732

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