EFFICACY OF ATARACTIC DRUGS IN CLINICAL ANAESTHESIA: A REVIEW

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COOLNESS and presence of mind under all circumstances, calmness amid storm, clearness of judgment in moments of grave peril, immobility and impassiveness are all synonymous with imperturbability or equanimity. These qualities were of the highest order to be attained by physicians in the opinion of Sir William Osler (1). In the three generations since Osler uttered his sermon on Aequanimitas, physicians have been trying to transfer these qualities to their patients because they know that mental stress and chronic anxiety aggravate physical debility and disease states.

For many years the clinician has employed such drugs as alcohol, barbiturates and other types of hypnotics, bromides, paraldehyde, and a variety of analgesic-sedatives, to calm the anxious patient. Success with these agents has been variable. Morphine is still the first choice for the relief of traumatic pain. Salicylate derivatives provide excellent relief from inflammatory and congestive pain and the associated mental anguish. Caffeine and amphetamine and their derivatives are still favourites for the relief of mental depression and fatigue. The addictive properties of most of these drugs is a serious problem, however. (The three most widely used drugs in the world have addicting properties—caffeine, nicotine and alcohol.)

During the past decade many new kinds of behaviour altering drugs have been introduced with great success. They not only suppress manic excitement and anxiety, but also counteract depression and promote stability and imperturbability (2). The term "Ataraxia" has been introduced by Fabing to describe this altered mood which can be produced by drugs.

Because the practising anaesthetist is in daily contact with patients who have major physical problems together with a strong psychic overlay of anxiety or depression, it is of the utmost importance that he becomes familiar with the growing variety of mood altering drugs. This knowledge will ensure their employment in a rational manner, to the advantage of the patient and the anaesthetist. Frequent review of experimental and clinical evaluations of these new drugs should be the only basis for their use in general clinical practice. The efficacy of each agent must be coupled with a precise knowledge of its multiple actions and of its main dangers, together with information on the experiences of others (3, 4, 5).

GENERAL CONSIDERATIONS

The anaesthetist who is alert to psychosomatic relationships realizes that mood and behaviour are greatly modified by the physical condition of patients and by their environment (6). Insight is usually more readily secured in patients who

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have mental problems, if their nutritional and physiological status are satisfactory. The nutritional status in the geriatric patient and in any patient with a chronic illness always requires more careful attention, especially in relation to vitamin and protein intake (7). For optimum nervous stability certain vitamins such as thiamine, pantothenic acid, ascorbic acid and nicotinamide seem to be necessary. Psychotic states are often improved by large doses of these substances, which also seem to be important in preventing degenerative changes in the nervous system.

Studies of the action of the ataractic drugs have increased the knowledge of the role of serotonin (5-hydroxytryptamine) in nerve conduction, the activity of nervous tissue and in cardiovascular homeostasis. The suggestion is that optimum nerve function depends on the ratio of intracellular to extracellular serotonin. When there is a relative increase in intracellular serotonin, there is increased tension, alertness, irritability and a tendency towards convulsive behaviour. On the other hand, a relative excess of extracellular serotonin is associated with central nervous system depression and withdrawal. Serotonin may be the most important regulator of the activity of the subcortical areas of the brain (8, 9, 10). Its importance in brain function is indicated by the observation that serotonin is affected differently by the various types of tranquillizer. Reserpine releases serotonin from cells in the central nervous system, especially in the brain stem. On the other hand, chlorpromazine has been found to inactivate serotonin which has been injected or which is in the circulation; while mepazine does not affect serotonin in the circulation. Chemical considerations associated with serotonin and its chemical relatives suggest the importance of the blood-brain barrier in connection with the peripheral administration of some of these drugs The blood-brain barrier is no specific structure but is a functional block to certain chemicals which seem to be easily dehydrogenated by brain cells as an adaptive protection to the organism as a whole This barrier may be overwhelmed by overdosage. The physiological action of these chemicals suggest, also, the importance of feed-back to the central nervous system from the periphery, particularly of proprioceptive impulses from muscles and joints This activity stimulates mental alertness and tension in much the same way as does hyperthyroidism (11).

Although the clinician cannot adequately control chemical and physiological factors in mental disturbance as yet, every attempt should be made to regulate the disturbing environmental factors. The ataractics can aid the anaesthetist to obtain a more satisfactory response to environment in mentally disturbed and psychoneurotic patients, as well as in those with the common anxiety response to operation (12, 13).

Differentiation of cortical neuroses into motor, sensory and mental forms is possible. Depending on the areas or structures of the cortex which are over-stimulated by impulse alterations in it, and in the hypothalamus and the thalamus, abnormal behaviour will differ in each individual. The determining factors depend on whether specific or non-specific discharges occur through cortical or subcortical structures of the brain. If abnormal discharges pass mainly through the sympathetic structures of the hypothalamus, a sympathetic or anxiety type

of neurosis appears. Such discharges through the parasympathetic system cause a different type of perturbance (peptic ulcer, spastic colon, etc.). These changes may be indicative of an altered balance of chemical substances in the brain (epinephrine, norepinephrine, serotonin, acetylcholine and histamine).

The primary role of ataractics in anaesthesia is to decrease the state of mental agitation, most probably by inhibiting in the subcortical reticular activating system the transmission of noxious motor, sensory and psychic stimuli to the cortex. They may also be effective by raising the threshold of response to reflex stimulation in the specific areas of the cortex, thalamus, hypothalamus, spinal cord, and certain highly sensitive reflex areas in other parts of the body (14). They also provide the physical and mental relaxation which is needed for development of "natural sleep." Present efforts to distinguish quantitatively and qualitatively the actions of the various drugs must proceed, therefore, in order to provide the clinician with a sound basis for the analysis of the areas of usefulness of each of the ataractics with particular reference to their effect on regulation of the autonomic nervous system.

The simplest approach to a review of these drugs is by classification according to their sedative activity. Insufficient data are available to present this with respect to the effect on endogenous serotonin. Two other approaches are available. One of these is based on the differentiation of sedation into hypnotic, psychotic and neurotic moieties (15). In this classification the hypnotic-sedative greatly depresses the cortex and thus raises the threshold of the nervous system to all sensory perceptions and enforces drowsiness and sleep (opiates, chloral hydrate, barbiturates). The psychosedatives help to control the agitation of psychotic patients and render disturbed patients more amenable to psychotherapy (reserpine, chlorpromazine, azacyclonol). The neurosedatives are useful mainly in anxiety and tension states associated with neurotic disturbances (ectylurea, meprobamate, hydroxyzine bromides) This classification in man is hindered by the marked overlapping of effects and the knowledge that no two patients will respond alike to a sedative

Another method of classification is the one most frequently used by the pharmacologist It depends, primarily, on the structura formulae of compounds. This is usually the best way to separate the various compounds. For the purpose of this review the ataractic drugs will be divided into five groups, mainly on the basis of their chemical structure, but also with due regard to their primary mode of sedation, as it is not always possible to correlate the activity of a drug with its chemical structure (e.g., azacyclonol and pipradrol). The groups are as follows: (*a*) alkaloids of rauwolfia; (*b*) phenothiazine derivatives and analogues based on chlorpromazine; (*c*) benzhydrol derivatives; (*d*) hydroxypropane derivatives; (*e*) miscellaneous neuro- and hypno-sedatives. The pertinent clinical and pharmacological data will be discussed and summarized under the above headings. The structural formulae of these compounds are shown in Figure 1. The trade name, efficacy in anaesthesia, average dose for premedication in anaesthesia (for patients in the age group 15–60 years, and in physical state I and II) and important reactions or dangers are summarized in Table I.

TABLE I

Trade name	Official and chemical name	Anaesthetic indications (mg.)	Clinical dose	Dangers and reactions
		RAUWOLFIA ALKALOIDS		
Serpacil (Ciba) Sandril (Lilly) Quiescin (Organon)	reserpine	Not useful in anaesthesia due to delayed action Psychosedative		Hypotension
Moderil (Pfizer) Raudixin (Squibb) Rauwiloid (Riker)	Rauwolfia Alkaloidal Fractions	Acute psychosis with excitement Compulsive drives Hypertension	0.25	Suicidal depression
Harmonyl (Abbott)	Deserpidine II—desmethoxyreserpine	Tachycardia		
		DERIVATIVES OF PHENOTHIAZINE		
Largactil (Poulenc)	Chlorpromazine	Psycho and neurosedative, sympatholytic	50–100 (oral)	Hypotension
Thorazine (S K F)	2 chloro-10-(3-dimethylamino-n-propyl)-phenothiazine hydrochloride	Nausea, vomiting, hiccoughs, pruritis Shivering Delirium Premedication Potentiate anaesthetics Prevent myocardial irritability Dilate coronaries Depress cardio-respiratory reflexes Facilitate hypotension and hypothermia Mild antisialogogue	25 (i m) 5– 10 (i v)	Tachycardia Skin allergy
Pacatal (Warner-Chilcott)	Mepazine 10-(N-methyl-3 piperidylmethyl)-phenothiazine acetate	Milder than chlorpromazine Anticonvulsant Parasympatholytic	100 (oral) 50 (i m.) 25 (i v)	Hypotension
Sparine (Wyeth)	Promazine 10-(3-dimethylamino-n-propyl)-phenothiazine hydrochloride	Milder than chlorpormazine	100 (oral) 50 (i.m.) 10 (i v)	Hypotension
Stemetil (Poulenc) Compazine (S.K.F)	Proclorperazine 2-chloro-10-(3-1-methyl-4-piperazinyl-propyl)-phenothiazine dimaleate	Anti-emetic Premedication Hypno and psycho sedative	10 (oral) 5 (i.m.)	Hypotension
Trilafon (Schering)	Perphenazine 1-(2-hydroxyethyl)-4-[3-(2 chloro-10-phenothiazyl-propyl] piperazine	Anti-emetic Premedication Hypno and psychosedative	10 (oral) 5–10 (i m., i v)	None
Phenergan (Poulenc) (Wyeth)	Promethazine N-(2-dimethylamino-n-propyl) phenothiazine	Antihistaminic Hypno and psycho sedative Anti-emetic Antisialogogue	100 (oral) 50 (i.m.)	None

TABLE I (*continued*)

Trade name	Official and chemical name	Anaesthetic indications	Clinical dose (mg)	Dangers and reactions
		DERIVATIVES OF HYDROXYPROPANE		
Myanesin (B.D.H.) Tolserol (Squibb)	Mephanesin 3-(2-methyl phenoxy)-1,2-propanediol	Muscle relaxant Pain due to muscle spasm Neurosedative in obsessional disorders	1 gm (oral) 1 gm (i.v.)	Nausea and vomiting Intravascular haemolysis Phlebothrombosis
Miltown (Wallace) Equanil (Wyeth)	Meprobamate 2-methyl-2-n-propyl-1,3-propanediol dicarbamate	Premedication Neurosedative in anxiety and tension states Muscle relaxation Hypnosis (somnolence)	800 (oral)	Skin allergy Addiction
(Lilly) Ultran (Lilly)	Phenaglycodol 2-p-chlorophenyl-3-methyl-2,3-butanediol	Premedication Neurosedative in anxiety and tension states Antispasmodic Anticonvulsant	600 (oral)	
		DERIVATIVES OF BENZHYDROL		
Levol (Horner) Suavitil (Glaxo)	Benactyzine hydrochloride B diethylaminoethyl benzilate hydrochloride	Premedication Neurosedative for psychomotor hyperactivity anxiety and tension states Antisialogogue Potentiate barbiturates	3 (oral)	None reported Contraindicated in depression and psychoses
Suvren (Ayerst) Covatin (Warner)	Captodiamine hydrochloride p-butylthiodiphenyl-methyl-2-dimethylaminoethyl-sulphide-hydrochloride	Premedication Neurosedative Psychosedative (depress irritability) Antispasmodic (smooth muscle) Potentiate barbiturates	100 (oral)	None reported
Atarax (Roerig) (Pfizer)	Hydroxyzine 1-(p-chlorobenzhydryl) 4-[2-(2-hydroxyethoxy-ethyl)] diethylenediamine dihydrochloride	Premedication Neurosedative for anxiety and tension states Antihistaminic	50 (oral) 25 (i.m.)	None reported
Frenquel (Merrell)	Azacyclonol alpha-(4-piperidyl)benzhydrol hydrochloride	Neuro and psychosedative for acute psychosis, toxic hallucinations, confusion and postoperative psychosis	10 (i.v.) (q 8 h)	None reported
Meratran (Merrell)	Pipradrol alpha-(2-piperidyl) benzhydrol hydrochloride	Psychomotor stimulant for post operative psychic depression	2 (i.v.)	Contraindicated in psychomotor agitation (danger of suicide)

TABLE I (*continued*)

Trade name	Official and chemical name	Anaesthetic indications	Clinical dose (mg.)	Dangers and reactions
Ritalin (Ciba)	Methyl-phenidyl acetate	Psychomotor stimulant Respiratory stimulant (analeptic)	30 (i.m.) 20 (i.v.)	Contraindicated in psychomotor agitation
	methyl-(alpha-phenyl-2-piperidyl)-acetate hydrochloride	Postoperative anaesthetic depression Morphine depression		
		MISCELLANEOUS SEDATIVES		
Hexamid (Nordmark)		Premedication Psychosedative	100 (i.m.)	?
	2,4,6-trioxohexahydro-5-diethylaminoethyl-pyrimidine	Potentiate anaesthesia Antisialogogue	50 (i.v.)	
Nostyn (Ames)	Ectylurea	Premedication Neurosedative for anxiety and tension	600 (oral)	None reported
	2 ethyl-cis crotonylurea			
Luminal (Winthrop Stearns)	Phenobarbital	Premedication (60 min. ante h.s.) Neurosedative	100 (oral)	Hangover excitement
	Sodium ethyl phenyl barbiturate	Hypnosedative Anticonvulsant		Skin allergy Nausea
Dormison (Schering)	Methylparafynol	Premedication (60 min. ante h.s.) Hypnosedative	500 (oral) 500 (i.m.)	Allergy Hepatotoxic?
	3-methyl-pentyne-ol-3	Anticonvulsant ?		Belching ~~Bad after-taste~~ Visual and speech disturbance
~~Placidyl (Abbott)~~	~~Ethylchlorvynol~~	~~Premedication (30 min. ante h.s.)~~ Hypnosedative	500 (oral)	None reported
	Beta-chlorovinyl-ethyl-ethynyl-carbinol			
Valmid (Lilly)	Ethinamate	Premedication (30 min. ante h.s.) Hypnosedative	500 (oral)	None reported
	1-ethinyl-cyclohexyl-carbamate	Neurosedative		
Doriden	Glutethimide	Premedication (60 min. ante h.s.) Hypnosedative	500 (oral) 250 (i.m.)	Nausea Skin allergy
	alpha-ethyl-alpha-phenyl glutarimide			
Noludar (Roche)	Methyprylon	Premedication (30 min. ante h.s.) Hypnosedative	300 (oral)	None reported
	3,3-diethyl-5-methyl-2,4-piperidinedione	Neurosedative		

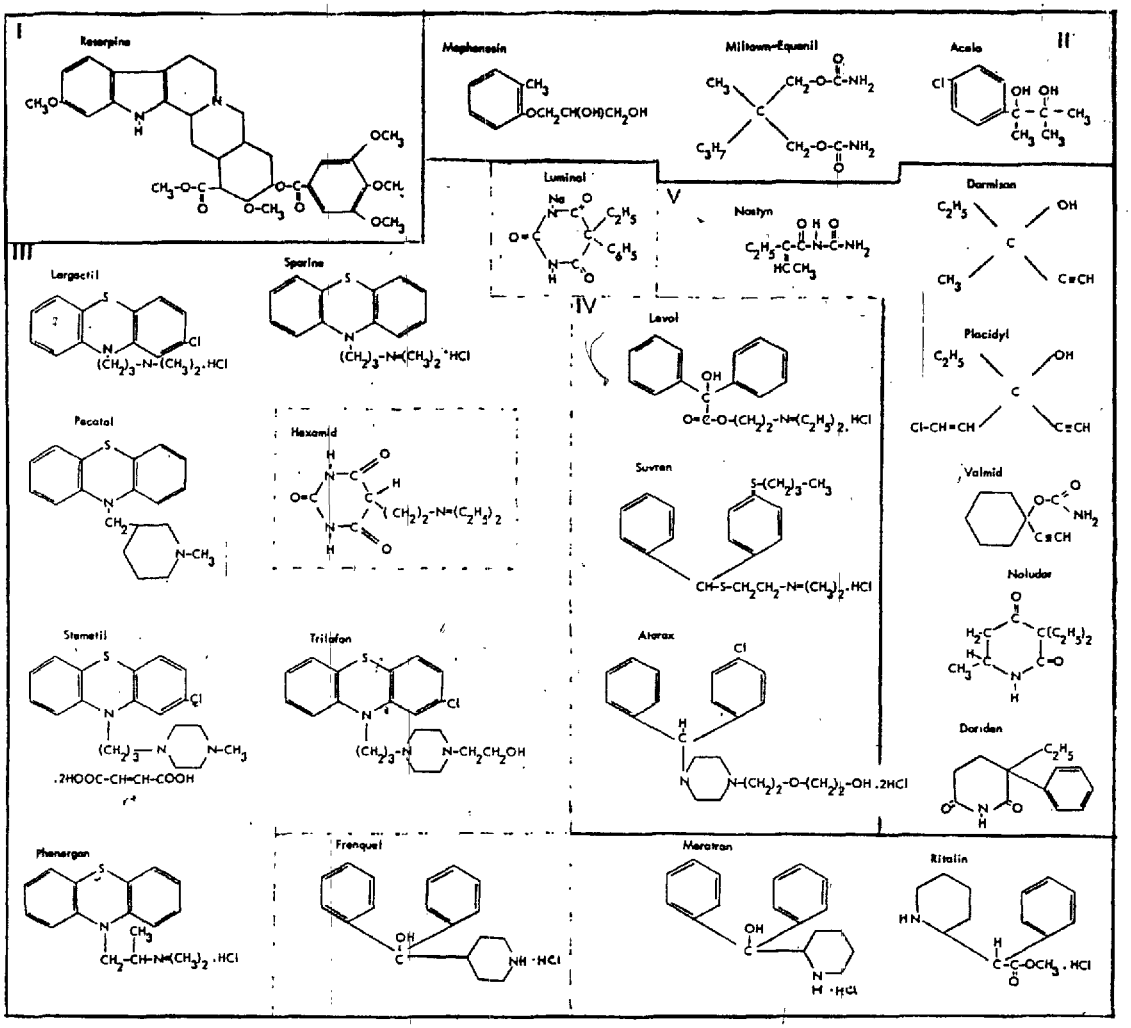


FIGURE 1. Comparative chemical structure of ataractic drugs.

DESCRIPTION OF DRUGS

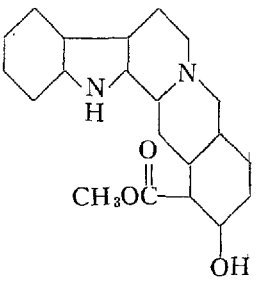
Alkaloids of Rauwolfia

The roots, leaves, and juice of rauwolfia plants were used from primitive times by the Hindus for relief of fevers, insomnia, dysentery, seizures and frenzy. The apocynaceous plant was named *Rauwolfia serpentina* in honour of Leonard Rauwolf who was a sixteenth-century botanist and physician. Modern pharmacological and clinical studies were reported from India beginning in 1931 (16, 17, 18). The Indians noted clinically that the powdered root of rauwolfia plants lowered blood pressure and quieted mania.

Reserpine is the most useful alkaloid of rauwolfia. It was isolated in 1952 by Schlittler and was found by Bein to have hypotensive and sedative action (19, 20). The first clinical reports on reserpine were published in 1954 (21, 22). Since then many clinicians have agreed on the value of reserpine as a hypotensive tranquillizing agent. The powdered whole root is also available as a tranquillizing agent for office practice and for producing a gradual, sustained lowering of blood

pressure in hypertension. It is claimed that the powdered whole root, satisfactorily standardized, gives activity not due to reserpine alone.

Reserpine is a white crystalline compound, soluble in alcohol and glycols, insoluble in water and sensitive to light in solution. It is a complex chemical compound containing an indole nucleus with several methoxy groups (see Table I). The structure is closely related to yohimbine:



Reserpine and the other alkaloids of Rauwolfia are readily absorbed from the alimentary tract and are distributed through the body. Their fate in the body is not known. Brodie and his associates indicate that reserpine acts by liberating serotonin from blood platelets, intestinal mucosa and the brain (9).

The powdered whole root of rauwolfia is administered orally in tablet form in doses of 50 to 100 mg. Reserpine is available in tablets containing 0.25 mg. each. The daily dose of reserpine varies from 0.1 to 1 mg., usually given orally. Clinical effects develop slowly but are significant and marked. Bradycardia develops first. This can be prevented with the solanaceous or synthetic antisialogogues (atropine, oxyphenonium). Blood pressure is reduced slowly in hypertension by central depression (hypothalamic?). Tension, emotional instability and over-aggressiveness are relieved at the same time, usually without causing drowsiness or sleepiness. No untoward effects are noted on the liver, kidney or blood cells. On the other hand, there may be nasal congestion and disturbance of appetite. Prolonged therapy may cause constipation. In some patients reserpine has been found to cause depression. *This may be serious enough to develop into suicidal tendencies.* Tolerance or addiction has not been reported. Allergic reactions are rare.

In office practice rauwolfia has been found to reduce complaints of dizziness, insomnia, excitability, irritability and anxiety. It may promote a sense of well-being among nervous individuals and reduce premenstrual tension and nymphomania. Outstanding has been the effectiveness of rauwolfia in anxiety and in hypertension associated with excitability. In all of these respects it is particularly useful in old people.

Its use should be carefully controlled clinically and its administration should be stopped promptly if depression or other untoward effects occur. If a surgical operation becomes necessary, it is well to discontinue therapy several days before the operation if general or spinal anaesthesia is to be used. If an emergency operation is required, 0.5 mg. of oxyphenonium and 5 mg. of methedrine may be administered intravenously before induction of anaesthesia. Because of the delayed onset of sedative action, this group of drugs has no specific place in clinical anaesthesia (23, 24, 25).

Phenothiazine Derivatives and Analogues based on Chlorpromazine

Chlorpromazine-hydrochloride was synthesized by Charpentier of Rhône-Poulenc Laboratories in France in 1951. The pharmacology of chlorpromazine has been widely studied in animals and in man during the past five years (26, 27, 28, 29, 30). It is a white crystalline powder, soluble in water with a pH of 5, and stable for a short period. It is quickly absorbed from the alimentary canal and distributed through the body. While its fate in the body is not yet known, it appears to be destroyed or eliminated in six or eight hours. The numerous side effects which may develop always follow prolonged use of the drug (31), and have never been recorded following a single administration.

Chlorpromazine depresses conditioned responses, antagonizes motion sickness and drug-induced emesis, depresses abnormal motor activity (shivering, hiccoughs, dyskinesia, myocardial irritability and produces tranquillity in the delirious and agitated patient. Parenterally, the most important effects are peripheral vasodilatation, mild hypotension, transient tachycardia and reduction of reflex irritability. Chlorpromazine is slightly antihistaminic and relaxes the tone of smooth muscles and spasticity in striated muscles

The anaesthetist must be wary of the orthostatic hypotension produced by this drug, and its potentiating effect on hypnotics, analgesics and anaesthetic agents calls for cautious management of anaesthesia. Body temperature is lowered slightly and a moderate to marked adrenolytic effect is evident when the drug is administered parenterally. When hypotension occurs, pressor drugs must be carefully selected (phenylephrine) and larger doses are required for an effective response. Pressor reversal effect occurs with epinephrine. It has no anticonvulsive action. The hypertensive action of serotonin is reduced by chlorpromazine (direct experiments show that chlorpromazine antagonizes serotonin). It also increases brain-stem content of adenosine-triphosphate Tolerance seems to develop to chlorpromazine on repeated oral administration

French investigators first noted the central depressive effects of chlorpromazine and its inhibition of psychic disturbances (32). Lehman and Hanrahan have published detailed accounts of the inhibiting effect of chlorpromazine on psychomotor excitement and manic conditions in man (33).

Clinical evidence shows the value of chlorpromazine in controlling nausea and vomiting due to a variety of causes, including drugs, radiation, pregnancy and motion sickness. In severe cases, effective control is quickly obtained by an intramuscular dose. For milder cases, or in children with viral gastritis, small oral doses every six hours may be satisfactory. If the drug cannot be tolerated orally by children, it may be given by rectal suppository

Chlorpromazine is most useful in controlling psychomotor agitation. It may also relieve hallucinations and delusions in schizophrenia. In depressive states clear benefit is *not* usually observed For improvement in psychotic patients, high doses usually seem necessary. This dosage should be reduced as soon as a beneficial effect is seen. In agitated senile patients small doses by mouth have been helpful.

Chlorpromazine relieves symptoms of several forms of dyskinesia (34); it some-

times helps also in controlling withdrawal symptoms in opiate and alcohol addictions. It has been used with great succcess as an adjunct to various analgesics in relieving the pain of cancer. In selected cases, chlorpromazine is useful as a preanaesthetic medication or as an adjunct to anaesthesia (35, 36, 37, 38). Preoperatively, it relieves anxiety, aids in controlling restlessness during spinal anaesthesia and reduces postoperative nausa, vomiting and delirium. It causes only slight reduction of salivary secretions (39). Chlorpromazine is very helpful in relieving persistent hiccoughs. It was also found to be of value in the conservative treatment of peripheral vascular disorders (40).

Undesirable effects of chlorpromazine are uncommon even when given orally or parenterally over a prolonged period. Its most unsatisfactory effect is the production of allergic reactions. This may even occur by contact sensitization among nurses or physicians. Fortunately, the allergic reactions clear promptly on stopping treatment or contact. In some patients, urticarial rashes may appear, while others may show gastrointestinal distress. An allergic-type of jaundice is the most serious untoward effect from chlorpromazine, but the incidence seems to be less than 1 per cent in patients on prolonged therapy.

The administration of chlorpromazine should be stopped on the appearance of any untoward symptom. It may usually be restarted safely after a week or so without any further untoward effect or allergic reaction. Chlorpromazine should not be used in the presence of liver disease and it is not wise to give it to a patient who is under the influence of hypnotics or alcohol. Patients requiring an operation and who are receiving chlorpromazine must be more carefully managed during anaesthesia. If the operation is elective, the drug should be discontinued a day before. If an emergency operation is required, physical measures should be employed to counteract the peripheral vasodilatation. For elective operations, fine judgment is required to select the proper dose for premedication (10-50 mg. intramuscularly) and for therapeutic measures during an anaesthetic (1-10 mg. intravenously) (41).

Mepazine (*Pacatal®*) was developed in Europe in 1953. It is a white crystalline salt which is photosensitive. It is rapidly absorbed following oral administration. The pharmacology of mepazine was first reported in 1954 (42). It is said to exert a selective regulatory action on the central nervous system, without inhibiting higher centres. The ability of mepazine to produce ataraxia without dulling of alertness is much milder than that of chlorpromazine. The most important effects of mepazine when used in pre-anaesthetic medication appears to be mild sedation without excessive soporific action, potentiation of anaesthetics and a balanced depression of the autonomic nervous system. Mepazine also depresses myocardial irritability, has moderate antipyretic properties, some anti-Parkinson effect, inhibits gastrointestinal contraction caused by acetylcholine or histamine, and has a mild mydriatic effect. It blocks effectively the salivary flow produced by pilocarpine, and decreases the pressor action of adrenalin but does not act as a serotonin antagonist. Mepazine is said to have a relatively weak anticonvulsant effect against chemically induced convulsions.

In summary, the pharmacological actions of mepazine are similar to those of chlorpromazine, but its effects on the parasympathetic nervous system are greater

while all other effects are milder. Hence it causes less haemodynamic disturbance while ataraxia is adequate (43, 44, 45, 46). Aside from hypotension, no serious side effects have been prominent. Allergic and haematologic disturbances are likely to occur, however, if prolonged therapy with large doses is employed.

Promazine (*Sparine®*). The structural formula of promazine is identical to that of chlorpromazine, except that it lacks the chlorine atom in the 2 position. It is a crystalline salt that turns slightly pink on standing. In most respects the acute actions of promazine are the same as those of chlorpromazine but are less potent The taming effect of promazine on monkeys is more predictable and consistent This differs from that produced by chlorpromazine in that the taming is less masked by depression Recovery from the effect of promazine is more rapid than with chlorpromazine because it is less potent. It has been found to control effectively symptoms of central nervous system excitation, to allay apprehension and anxiety and to calm the acutely agitated patient It is indicated in the management of a variety of acute mental disturbances. It appears to be best suited for alcohol-induced inebriation syndromes such as delirium tremens, acute hallucinosis, acute tremulousness as well as agitation due to various psychoses, and for withdrawal symptoms of drug addiction (47). Promazine is not at the present time recommended for use in chronic mental disturbances, but may be used to control acute episodes of hyperactivity Administration should be discontinued when these disturbances are under control (48, 49, 50).

Patients with delirium tremens respond as dramatically to promazine as to chlorpromazine: they become calm, more rational and in most instances sleep normally following a single intravenous dose. However, there is less likely to be serious vasomotor disturbance with promazine Similar responses are obtained in patients with acute hallucinosis. When the acute phase is controlled by intravenous therapy, the patient may be maintained on oral or intramuscular doses until improvement persists (limit therapy to two weeks).

In acutely disturbed psychotics, the intravenous administration of promazine (25 to 50 mg.) controls the acute symptoms The tranquil state is then maintained by oral or intramuscular administration. Sleep from which the patient can be aroused easily follows this treatment, and on maintenance therapy the patient remains quiet, calm and co-operative. Hallucinations when present are either abolished or become less frightening.

Side effects of promazine include drowsiness and transitory postural hypotension. Dizziness without marked change in blood pressure has been reported following its use in alcoholics, whereas with chlorpromazine there is frequently a marked hypotension. Allergic skin reactions, alterations in peripheral blood cells, hepatic dysfunction and extrapyramidal symptoms resembling Parkinson syndrome have been uncommon. Seizures are being reported with increasing frequency when high doses are taken. Cases of agranulocytosis have been recorded recently, but are as rare as with chlorpromazine.

As the use of this drug increases, the number of toxic reactions appear to be increasing, but they do not seem to be as numerous or as severe as for chlorpromazine. This may reflect a more conservative and cautious approach to intensive therapy based on the experiences with the latter.

The amount, route of administration, and frequency of administering chlorpromazine, mepazine, or promazine, should be governed by the degree of central nervous system excitation present and the patient's initial response. The oral route of administration should be used whenever possible, but when nausea, vomiting or lack of co-operation is evident the drugs should be given intravenously or intramuscularly. When given by these routes the patient should be closely observed until the peak action of their effect is subsiding. In general, doses of 50 to 100 mg. of mepazine or promazine are sufficient when given intravenously. If the desired calming effect is not apparent within 5 to 10 minutes, a smaller dose may be repeated. Once the desired effect is obtained the dose may be given intramuscularly or orally in 25 to 200 mg. doses at 4- to 6-hour intervals, depending upon the previous response of the patient. It is seldom necessary to administer more than 20 mg. of chlorpromazine intravenously for similar effects, as it is about twice as potent as mepazine and promazine.

Proclorperazine and perphenazine are aminophenothiazine derivatives with a wide range of activity Because of their reported efficacy in both mild anxiety and severe psychotic reactions, they have been termed "broad spectrum tranquillizers."

Proclorperazine was developed by the combined effort of Rhône Poulenc Specia (Stemitil®) and S K F. Laboratories (Compazine®). It has been used for a wide variety of mental and emotional conditions (51): anxiety, agitation, agitated depression, tension, confusion, restlessness, senile agitation and post-alcoholic states. Anxious or agitated patients become calm on this medication. Tension is relieved and replaced by mental and physical relaxation. Patients become quieter and more co-operative, sleep soundly at night and remain alert during the day.

Proclorperazine was found effective when the presenting symptoms were both mental and emotional and when these psychic conditions complicated somatic disorders It is five to ten times more potent than chlorpromazine. At the present time it is recommended for relatively short therapy (not longer than two weeks). In clinical trials, small doses administered orally have been found to be highly effective as a psycho- and neuro-sedative. It is also a potent anti-emetic in a wide variety of conditions (52)—pregnancy, viral gastro-enteritis, postoperative conditions, duodenal ulcer, terminal cancer, meningeal inflammation, radiation sickness, migraine and tension headaches. Side effects include mild drowsiness, some dizziness and mild skin reactions. Extrapyramidal symptoms are neither common nor severe and disappear upon withdrawal of the drug

The potentiating action of proclorperazine is not as great as that of chlorpromazine. However, if sedative agents such as alcohol, opiates or barbiturates are used in conjunction with it, their amounts should be greatly reduced. Proclorperazine is contraindicated in comatose or greatly depressed states, and is probably best avoided in the presence of liver disease.

The dosage recommended for night sedation is 5 to 10 mg. by mouth and for preoperative sedation 5 mg may be given intramuscularly one hour before anaesthesia.

Perphenazine (*Trilafon*®) was introduced by Schering Corporation This phenothiazine derivative is about twice as potent as proclorperazine and ten to fifteen times more potent than chlorpromazine. It appears to be equally as

effective as an ataractic and an anti-emetic. The advantages claimed are that it does not cause hypotension in the geriatric patient, and does not produce allergic reactions, or alterations in liver function as frequently as does chlorpromazine (53). In anaesthesia it may be used for premedication as described for proclorperazine. A very potent anti-emetic effect is produced by 5 mg. intravenously without marked depression of blood pressure or respiration.

As for the other phenothiazine derivatives described, proclorperazine and perphenazine should be administered with discrimination and their use should be attended by careful and regular observation. Since they are potent phenothiazine derivatives, the patient receiving them should be under close observation for any signs of significant blood changes or other toxic manifestations. If extrapyramidal symptoms or haematologic changes appear, the drugs should be discontinued. Their potent anti-emetic action may mask signs of overdosage by other drugs (e.g., digitalis) or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumour

Extensive clinical trial is still required to prove whether these two agents have any advantage over other phenothiazine derivatives now on trial. Their employment in anaesthesia should be restricted to premedication in the anxious or agitated patient, and to use as an anti-emetic

Promethazine (*Phenergan®*) One of the first aminophenothiazine derivatives to show great promise as a therapeutic agent was promethazine (54, 55). It is a white crystalline powder which is practically odourless. It is soluble in boiling absolute alcohol Although promethazine was marketed in this country in 1950, it was not until 1954 that its great potential clinical value was recognized (56, 57). Since then an ever wider clinical efficacy has become evident, as this derivative has practically no disturbing side effects or toxicity in therapeutic doses (58, 59, 60, 61)

Promethazine has a wide range of therapeutic effects which are highly desirable in pre-anaesthetic medication In addition to its potent antihistaminic activity (which is two to three times as great as any previous such agent marketed), it is an efficient hypnosedative, potentiates anaesthetic action slightly and has adequate activity as an anti-emetic and an antisialogogue (39). These actions are not accompanied by depression of vasomotor tone and reflex activity—which are considered to be undesirable effects of the other phenothiazine derivatives.

Promethazine promises to be acceptable for general use in pre-anaesthetic medication because it potentiates the sedative effects of small doses of barbiturates and meperidine, and has no significant effect on blood pressure homeostasis, pulse rate or respiration Dose recommended is 100 mg. by mouth at bed time and 25 mg intramuscularly preoperatively, combined with reduced doses of a barbiturate and scopolamine. In children excellent preoperative sedation is achieved with smaller doses (60). To date, promethazine remains the most efficacious phenothiazine derivative for use in anaesthesia premedication

Derivatives of Hydroxypropane

Mephenesin (*myanesin®*). One of Berger's early contributions to our present knowledge of the ataractic drugs resulted from his studies of the glycerol ethers

in 1946 (62). Mephenesin, an aromatic glycerol ether, was clinically the most important drug in this group. This compound is an odourless white crystalline powder which dissolves poorly in water, but is freely soluble in ether and ethanol. When taken by mouth (elixir form), or injected intravenously in 1 to 2 gm doses, rapid absorption and distribution occur. Selective depression in the subcortical brain stem and depression of spinal polysynaptic transmission is produced. This causes a marked decrease in skeletal muscle tone and spontaneous activity, without loss of consciousness or disturbance of mental activity. Mephenesin also protects against convulsions due to strychnine and against electroshock seizures. It does not affect voluntary motor power and sensation (63).

In clinical practice it is used to relieve muscle spasm, and as an adjunct to the treatment of acute anxiety states and obsessional disorders. However, it is sometimes dangerous to take by mouth as it produces anaesthesia of the oropharynx and may facilitate aspiration of food Its use is limited also on account of its transient duration of action.

Its importance as a muscle relaxant in anaesthesia was short-lived, as it is not as efficacious as curare and related drugs now in use (64). Its present use is limited to treatment of muscle spasm and to behaviour disorders resulting from organic brain disease in children (65). The renewed interest in this drug, initiated by Berger, led to the synthesis of such important ataractics as meprobamate and hydroxyzine.

Meprobamate (*Miltown®*, *Equanil®*). Berger found marked sedative and muscle-relaxing effects from meprobamate (66). This drug has muscle relaxant actions similar to those of mephenesin, but of greater potency and longer duration It also antagonizes strychnine and metrazol convulsions. It produces a reversible flaccid paralysis of skeletal muscle without affecting the heart, respiration or autonomic functions Its action has been localized to the multi-neuronal reflexes. The clinical efficacy of meprobamate lies in its marked sedative action. The drug is ordinarily given in tablets each containing 400 mg, four times daily. When sedative effects are observed, the dosage should be reduced, and if improvement continues the drug should be withdrawn (67,68).

Meprobamate is useful as a sedative in anxiety, but is less effective in manic states. It is helpful as an adjunct to direct psychotherapy. It aids in clearing behaviour problems due to anxiety, conversion-hysteria and it is helpful in withdrawal symptoms of alcoholism. Meprobamate is not useful in the psychoses. It promotes restful sleep and general muscular relaxation without depression or hangover. It aids in clearing anxiety, tension-headache and neurogenic skin conditions or abdominal distress. It aids generally in reducing psychic tension, irritability and restlessness.

There are hazards which occasionally accompany the use of this drug, even on single administration (69). Hypersensitivity and allergic reactions, and acute non-thrombocytopenic purpura have been reported. These are probably quite rare The increased frequency of such reports may be attributed to the very extensive and uncontrolled use of this drug.

Although meprobamate may be classed as an ataractic, its use should be restricted to patients with mild anxiety and emotional instability. In anaesthetic

practice it is of value when given alone for night time sedation (800 mg.) and for pre-anaesthetic sedation (400 mg. intramuscularly) combined with an antisialogogue (70).

Phenaglycodol (*Acalo®, Ultran®*) is a new chemical compound derived from butanediol which was synthesized recently in the Eli Lilly Research Laboratories. It is a stable compound which is relatively insoluble in water, but quite soluble in ethanol and oils.

This type of compound was found to possess anticonvulsant and hypnotic activity. During trials of this drug as an anticonvulsant in children it was noted that there was marked improvement in their behaviour problems. This led Slater and associates to further studies on animals, which revealed that it had muscular relaxing effects similar to those of mephenesin (intraneuronal blocking effect) (71). In animal studies the compound exhibited selective depressant activity on polysynaptic pathways at spinal and superspinal levels. It also caused sedation and depression of arousal responses similar to those produced by barbiturates. The depression of spontaneous activity and mental tranquillity was not accompanied by effects on respiration, blood pressure or the electrocardiogram. This indicated that the drug might be efficacious as an ataractic of the neurosedative type.

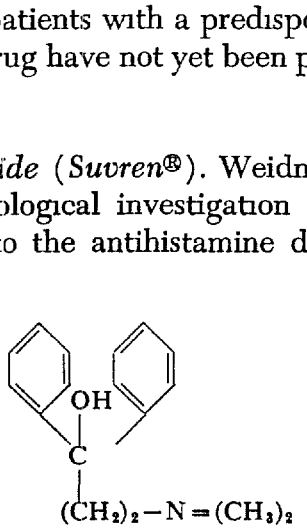
Reiten has compared the effects of phenaglycodol and meprobamate on psychological tests in human volunteers and patients (alertness, attention, reaction time, etc.) and found no adverse affect with either (72). This drug does not potentiate the hypnotic action of barbiturates nor does it produce a measureable or demonstrable relaxation of skeletal muscles in patients.

Clinical evaluations of this drug, which are in progress, indicate that it is of value for alleviating emotional tension without producing hypnosis. For pre-anaesthetic medication of the very tense patient, it may be of value in the dose of 600 mg combined with a barbiturate at bedtime.

No contraindications or side effects of a serious nature have been observed with this drug to date. Mild nausea, dizziness and gastric irritation have been reported when it was used for daytime sedation. It has no cumulative action. Clinical trials indicate that it is useful in the treatment of alcohol withdrawal and in the management of patients with a predisposition to alcoholism. Extensive clinical evaluations of this drug have not yet been published.

Derivatives of Benzhydrol

Captodiamine hydrochloride (*Suvren®*). Weidmann and Peterson reported on the chemical and pharmacological investigation of 37 compounds which were closely related chemically to the antihistamine diphenhydramine hydrochloride (Benadryl®) (73).



These investigators were interested in this group of antihistaminic drugs because many of them exhibited potent sedative and hypnotic effects. Promethazine and diphenhydramine had previously been reported to have the most potent sedative-hypnotic activity in this class (74).

By changing the molecular structure, they were able to increase the sedative, and decrease the hypnotic and anti-histaminic actions. One of the compounds which they studied was captodiamine hydrochloride. They found the following pharmacological properties. It possessed sedative activity which was three to four times that of diphenhydramine and promethazine. The sedative action was believed to be mediated through the higher centres in the cortex of the brain It also possessed a very potent spasmolytic or relaxing effect on smooth muscle. The action was like that of papaverine, but four to five times greater. It possessed no hypnotic effects, even in very large doses. It had no appreciable antihistaminic or anticholinergic effect, and did not cause hypotension.

No toxic effects on the haemogram have been reported. It has been tested in conjunction with several of the commonly used barbiturates and other hypnotics and does not produce a true potentiation of their activity. Captodiamine probably dilates the coronary vessels and exerts a powerful positive inotropic effect (increases the strength of muscular contraction) on the heart. The heart rate is unaffected. It has no affect on blood pressure or respiratory rate and does not possess any analgesic or anticonvulsant affects. It is particularly recommended for sedation in patients with anxiety, unrest and nervous tension when hypnosis is not desired, when long-term medication may be necessary and when smooth muscle relaxation without depressing normal tone of skeletal muscles is desired. This drug is not suitable for the treatment of severe psychosis. The dose recommended for night sedation is 50 to 100 mg. by mouth (75). Clinical evaluation in anaesthesia premedication has not yet been reported.

Benactyzine hydrochloride (*Levol®*, *Suavatil®*) was first described in Switzerland in 1936. In 1955 Jacobsen and others in Denmark found that it relieved anxiety in psychoneurotic patients (76, 77). Chemically it was closely related to diphenhydramine. It had a marked potentiating effect on general anaesthesia produced by intravenous barbiturates. It had a potent antispasmodic effect on the smooth muscle of the colon. Its anticholinergic action was found to be about twenty times that of chlorpromazine, and its antagonistic action to serotonin was approximately the same as that of chlorpromazine. As a histamine antagonist it was ten times less active than chlorpromazine and twenty times less active than diphenhydramine It produced electro-encephalagraphic changes similar to those seen with atropine. Animal experiments show that it was dangerous to combine this drug with electroconvulsive shock treatment. It was found to have anticholinergic properties with a selective action on the hypothalamus. Its atropine-like action in man was mild. It appeared to raise the emotional threshold of the higher brain centres to irritant stimuli by blocking the nerve pathways to the hypothalamus, thus preventing reaction to external stimuli which normally cause strain and tension. It had no hypnotic activity. Serious toxicity has not yet been reported, but side effects—including dryness of the mouth and paralysis of accommodation—appear to occur frequently and are annoying (76).

Reports on its value in clinical medicine have been mixed Some question its value in neuroses and in marked anxiety and tension. Others have reported it to be effective in anxiety, obsessional states, psychogenic asthma and eczema, alcoholic addiction and as an adjuvant to psychotherapy. It combines well with barbiturates and may be used in ambulant patients. The recommended dose is 1-3 mg. orally. It is most useful in diffuse non-specific anxiety and tension, and less so in phobias and hysteria. It is contraindicated in depression and psychosis (77, 78, 79, 80, 81). No reports have appeared regarding its use in premedication for anaesthesia.

Hydroxyzine (*Atarax®*) belongs to the group of mild ataractic agents (neurosedative). It contains a p-chlorobenzhydrol structure as do both chlorocyclizine —an antihistamine, and meclazine—an antinauseant. Hutcheon observed that intravenous injection of hydroxyzine causes a transient fall in blood pressure, an increase in coronary blood flow and suppression of epinephrine-induced ventricular arrhythmias. He also observed an inhibition of the pressor response to epinephrine in cats under pentobarbital anaesthesia (82). Hydroxyzine has been found to be a potent antihistamine and serotonin antagonist. It does not block the change induced in smooth muscle by acetylcholine and does not prevent histamine-induced depressor responses in anaesthetized animals. It markedly prolongs the sleep induced by intravenous barbiturates and prevents electroshock seizures, but does not prevent metrazol and strychnine convulsions. It appears to increase significantly the convulsant and toxic effects of strychnine. It does not antagonize hyperexciteability of tendon reflexes as does meprobamate. Changes similar to those produced after atropine occur in the electro-encephalogram. Rhesus monkeys treated with hydroxyzine respond with a disinterested state and catatonia similar to that seen with chlorpromazine and promazine (83).

In patients it produces a state of mental and physical relaxation, and relief from emotional tension (84, 85). No abnormalities in the blood or in kidney and liver function have been reported as yet. It has no significant effect on respiration, blood pressure or pulse rate It is recommended in a dose of 25 mg. (intramuscularly) for premedication of surgical patients on the basis of its sedative and anaesthetic potentiating property.

Pipradrol and Azacyclonol (*Meratran® and Frenquel®*). Brown and Werner reported on the interesting actions on the central nervous system of some piperidyl-benzhydrol derivatives (86). These agents illustrate the importance of relatively slight changes in chemical constitution in determining significant differences in biological activity.

Pipradrol is a bitter crystalline compound which is relatively well absorbed from the alimentary canal. Its fate in the body is unknown. It seems to be destroyed or excreted within four to six hours. Its effects are chiefly on the central nervous system. According to Himwich it stimulates the central reticular substance of the brain. This is followed by cortical stimulation (87). Pipradrol does not increase blood pressure and has no effect on the gastro-enteric system or on respiration.

Since pipradrol is a general central nervous system stimulant, it has been used therapeutically to counteract mild depressive states and to counteract postanaes-

thetic and chlorpromazine depression (88). It apparently has no significant action on the autonomic nervous system and its use is not followed by wakefulness. It seems to be especially effective in the control of motor tic syndromes. Patients suffering from torticollis are often aided by treatment with pipradrol and it helps to relieve lumbar muscle spasm and low back pain. Its clinical value in these conditions is indicated by reports by Fabing and others (89, 90, 91).

No untoward side effects and no toxicity have been reported. The drug is administered orally in tablets each of 1 mg. 3 to 6 times daily. *It must never be given to a patient with psychomotor excitement, as this has led to suicide.*

Azacyclonol. In studying the action of related compounds, Fabing observed that the gamma isomer of pipradrol had quite different effects (92). In azacyclonol the nitrogen in the piperidine ring has been moved over two positions from that which it occupies in pipradrol. The resulting compound is a bitter white crystalline substance, partially soluble in water and rapidly absorbed from the alimentary tract. It is excreted or destroyed in four to six hours. This compound causes depression rather than stimulation of the central nervous system. It is in fact an antagonist of pipradrol, as well as of other central stimulating agents such as amphetamine or cocaine. Azacyclonol potentiates the depressant action of hypnotic and analgesic drugs. It is itself a relaxing agent and has insignificant toxicity on single administration (93).

Clinical trials indicate that azacyclonol is useful in acute schizophrenic conditions. It has an antagonistic action in model psychoses produced by lysergic acid diethylamide or by mescalline. The name Frenquel was given to it because of its ability to quell frenzy (92).

Azacyclonol may be useful in controlling the symptoms of acute schizophrenia and toxic hallucinations in a dosage of 10 mg. intravenously every 8 hours. It is not helpful in chronic schizophrenia or in senile or alcoholic patients with hallucinations, unless it is combined with other forms of drug therapy. Azacyclonol has no effect in depressive states or in obsessive-compulsive disorders. It does not aid in handling anxiety conditions (94).

Both pipradrol and azacyclonol require much more extensive study under controlled clinical conditions in order to indicate clearly their usefulness. In relation to anaesthesia, pipradrol may be of value in the management of severe psychic depression, whereas azacyclonol may be of value in the initial control of marked confusion and agitation in the postoperative period.

Methylphenidylacetate (*Ritalin®*). Meier has developed another interesting behaviour-altering drug which has the generic name methylphenidylacetate. It is a white crystalline compound soluble in water with a pH of 3 in 10 per cent aqueous solution. It is quickly absorbed from the alimentary canal. Methlyphenidylacetate is a central nervous system stimulant similar to pipradrol. Doses of 1 mg./kg. in experimental animals cause an increase in spontaneous activity with maximum restlessness in about an hour and with gradual recovery without untoward effects in about two hours. Against short-acting barbiturates it has an analeptic effect and counteracts respiratory depression due to morphine. There is little action on smooth muscles, on the cardiovascular system, or in circulating blood. No toxic effects have been observed (95).

It has been used in treating reserpine-induced depression and for markedly deteriorated chronic schizophrenic patients. Many showed significant clinical improvement. No untoward effects were noted and there was no interference with sleep (96, 97, 98). Its main value in anaesthesia is in the treatment of respiratory depression due to narcotic-analgesics and postanesthetic depression.

Miscellaneous Sedatives

Hexamid. Clinical trial with hexamid, a barbiturate acid derivative prepared by Nordmark Werken in Germany, has shown that this substance is not hypnotic, but possesses ataractic qualities similar to that of chlorpromazine. In animal experiments it was found to have half the toxicity, but a slightly greater duration of action than chlorpromazine. This drug has analgesic anticonvulsant and antisialogugue properties, but has no significant effect on the circulation, respiration, body temperature or blood coagulation. When injected subcutaneously it produces local anaesthesia.

Subcutaneous and intravenous injections of 25 to 50 mg. have similar affects in man. These appear in about five minutes with subcutaneous injection and in one minute after intravenous injection, and are: dryness of the mouth, a feeling of warmth, lack of power of concentration and initiative, flight of ideas, a feeling of well-being (sometimes euphoria) and a decrease in sensitivity to pain. The response lasts for one to one and one-half hours. There is also a variable decrease in accommodation, accompanied by diplopia, and difficulty in speaking and calculating. The pulse rate falls about 20 to 25 per cent, but the blood pressure remains unchanged. The respiratory rate and amplitude are not affected and there is a minimal decrease in vital capacity. Muscular power, as measured by the dynamometer, is reduced 10 to 15 per cent. Hexamid, in the same dosage and by the same route of administration, has a shorter and somewhat milder action than chlorpromazine, particularly as far as the patients' initiative and ability to concentrate are concerned. The sensitivity to pain is reduced to about the same extend by both drugs and reduction in muscular power is about the same. Hexamid dries salivary secretion to a greater extent, the feeling of well-being is more marked and it causes bradycardia rather than the tachycardia seen with chlorpromazine.

Hexamid is more potent than mepazine, particularly in its sedative and antisialogogue properties Its effect on the circulation is the same as mepazine. Unlike chlorpromazine and mepazine, it has no anti-emetic effect.

Hexamid appears to have a wide therapeutic margin. Five times the usual dose (250 mg. intramuscularly) causes light sleep and amnesia for the period of premedication, and anaesthesia is without other disturbance. The recommended dose of hexamid is as follows: for premedication 50 to 100 mg. subcutaneously or intramuscularly one hour before operation. This is combined with the usual doses of meperidine, but the belladonna derivatives are omitted. No toxic effects have been reported as yet Hexamid is compatible with all anaesthetics and ancilliary drugs (99).

Ectylurea (*Nostyn®*) is an ataractic which was investigated by Pindell and associates in 1953 (100), and introduced clinically by Ferguson in 1956 (101).

It relieves everyday apprehension and anxiety in a wide dose range without impairing mental alertness or producing drowsiness or hypnosis.

This drug is an almost insoluble, white, crystalline compound prepared by dehydrobromination of carbromal. It is readily absorbed from the alimentary tract. Sedation with this drug occurs in 15 to 30 minutes and last several hours. Only in a very large dose does this drug produce sub-hypnosis or a state of profound depression. Its wide dose range between sedation and hypnosis indicates a much greater margin of safety than with existing sedatives. Caffeine given before or after this drug does not alter its sedative effect It does not slow respiration beyond that seen during sleep and there is no effect on blood pressure or pulse rate. It has no anticonvulsant, analgesic or antispasmodic activity.

Ectylurea is recommended as a mild neurosedative (300-600 mg. at bedtime) which relieves tenseness and anxiety without causing depression, drowsiness or motor incoordination. Much larger doses are used for the management of psychotic patients. This produces more potent effects than meprobamate, but is less effective than reserpine or chlorpromazine. Toxic reactions have not yet been reported with long-term therapy.

Phenobarbital Sodium (*Luminal®*) and other barbiturates. Barbituric acid derivatives have enjoyed great popularity for premedication for many years because of their great efficacy as sedative-hypnotics and anticonvulsants. The large number of side effects which accompany the use of these drugs has led to their gradual replacement by other agents

The most commonly used barbiturate derivatives for pre-anaesthetic medication are phenobarbital, pentobarbital and secobarbital. Natural idiosyncrasy often occurs. This is marked by hangover, inebriation, excitement or neuralgic-type pain. Excessive hypnosis, lassitude, nausea and vomiting and diarrhoea are frequent. One-third to one-fourth of the hypnotic dose usually produces sedation, but it is difficult to predict as this response is variable in the individual patient. These drugs should not be prescribed without an analgesic in the presence of pain as the patient usually responds with excitement and delirium instead of tranquillity Psychoneurotic patients, especially, tolerate this type of sedation poorly. Many patients are allergic to the barbiturates and respond with swelling of the face or erythematous dermatitis. Addiction to barbiturates is relatively common and may be difficult to detect. Patients with renal or liver disease should not be given the barbiturate derivatives, which depend on these organs for degradation and excretion. Non-specific contraindications to barbiturate sedation include fever, hyperthyroidism and heart failure (102, 103).

Barbiturates are usually given as a 100 mg. oral capsule for a pre-anaesthetic hypnotic, and may be repeated by intramuscular injection one hour before induction of anaesthesia. Secobarbital and pentobarbital are also given intravenously as a sedative-hypnotic during regional anaesthesia. They are also used as an intravenous anaesthetic supplement for hypnosis, but they are unsatisfactory for this purpose as the patients tend to sleep far too long (35).

Methylparafynol is an unsaturated aliphatic carbonal (104) which was introduced by the Schering Corp. It is an orally potent, quick-acting hypnotic with anticonvulsant properties (105). It induces natural restful sleep from which

patients awaken alert and refreshed without drug hangover. Methylparafynol produces no respiratory depression and may be used in the presence of cardio-respiratory and broncho-pulmonary disorders when barbiturate hypnotics are contraindicated. Dosage recommended is 500 mg. by mouth, 15 minutes before sleep.

No adverse effect on the blood, kidney or liver function has been reported. Because of a potentiating effect, methylparafynol should not be given with large preoperative doses of barbiturates Numerous physical and mental disturbances have been reported with this sedative. An unpleasant breath and after-taste also follows ingestion. Reports indicate that it is a satisfactory sedative in the young and in the aged, but it should be used with some caution as a few cases of poisoning have been reported (105-109).

Ethylchlorvynol (*Placidyl®*) is a new non-barbiturate hypnotic of tertiary unsaturated carbinol which was recently introduced by the Abbott Laboratories. This drug was the most active of a series of chlorinated carbinols with sedative effects (110, 111). It is said to exhibit a hypnotic effect superior to that of the unhalogenated acetylenic carbinols. The drug has special usefulness for ordinary insomnia due to tension, mild anxiety, mild excitement or agitation. For pleasant induction of sleep at bedtime the usual dose is 500 mg. This dose induces sleep in approximately 15 to 20 minutes, with an average duration of about 5 hours. When patients are awakened from sleep, they are alert and mentally clear and have no ataxia, nervousness, drowsiness or hangover There are apparently no haematologic or liver function changes during administration of ethylchlorvynol. There are no observed effects on the pulse, blood pressure, respiration, blood or urine There are no reports available of its clinical use for anaesthetic premedication

Ethinamate (*Valmid®*), which was introduced by Eli Lilly Research Laboratories in 1953, is also a non-barbiturate hypnotic derived from tertiary unsaturated carbinol The primary indication for this drug is simple insomnia caused by mental unrest, excitement, worry, apprehension, or extreme fatigue Ethinamate is recommended for persons who are hypersensitive to barbiturates, and also, because of its very short action, for patients who awaken in the early morning hours and cannot get back to sleep. The usual dose is 500 mg. taken 15 to 20 minutes before retiring. The duration of sedation with this dose is about half that of secobarbital. Ethinamate has caused no demonstrable effects on the brain, blood, liver, kidneys or other body organs. It does not cause halitosis, nausea or skin rash.

Ethinamate should not be employed alone for insomnia due to pain, severe itching or coughing. It does not potentiate analgesics or other sedatives, and in a hypnotic dose it does not affect the blood pressure, pulse rate or respiration. No allergic manifestations or serious toxic reactions have been reported (112, 113).

Glutethimide (*Doriden®*), which was introduced by Ciba Pharmaceutical Products, Inc., is an oral non-barbiturate hypnotic-sedative. In the past few years it has become the most widely used sedative of this group. It is not soporific when given as a sedative and seldom causes morning hangover when given as a nighttime hypnotic (114). When given for insomnia its onset action is 15 to 20 minutes,

and it provides 4-8 hours of sound dreamless sleep. It is well tolerated by elderly neuro-psychiatric patients and by those with cardiovascular disease in whom the barbiturate sedatives may be poorly tolerated or contraindicated (115). It does not cause respiratory depression or alter blood pressure or pulse rate in therapeutic dosage (250-500 mg.). Prolonged administration has no effect on the blood picture or liver function (116). A number of suicides have been reported. In these cases 10 gm. or more were taken (117, 118).

One gm. given the night before and repeated one and a half hours before anaesthesia gives satisfactory sedation. Short-term administration does not cause gastro-intestinal or other disturbances. Skin rashes have been reported after prolonged administration

Methyprylon (*Noludar®*), introduced by Hoffman-La Roche, Inc., is a non-barbiturate sedative hypnotic, derived from piperidine dione (119). Extensive clinical trials indicate that it provides relief of insomnia in approximately half an hour, and restful sleep continues for an average of six to seven hours (120-124). After this sedation, the patient generally awakens refreshed without lethargy or hangover. It is particularly recommended for relief of nervous insomnia as it causes a mild central depression (125). It is also useful for daytime nervous tension. When sleeplessness arises from pain, methyprylon should be given in conjunction with an analgesic.

The recommended dose for premedication is 300 mg. half an hour before retiring. No alteration in blood pressure, pulse rate or respiration occurs, and the prolonged administration of large doses did not produce toxic effects on the blood (126, 127). Gross overdosage, however, leads to fatal poisoning (128).

Comments

The most important information for the anaesthetist who employs these new drugs is first; the potency, range of activity, effect on vital signs and the incidence of allergic reactions for each compound. This knowledge will assist in the selection of dosage for a particular situation. Secondly, the ability of the compound to potentiate the sedative, hypnotic, analgesic or muscle relaxant activity of other drugs employed in anaesthesia; and thirdly the variability of effect to be expected with each compound—since the effect of some drugs shows a narrow range of response while most drugs are notorious for the great variation of individual response even in healthy subjects (129).

Knowledge of these points will be helpful in predicting whether a particular dose is likely to produce the desired effect, or undesirable side effects and toxic reactions. It will also assist the anaesthetist to avoid what are frequently termed hypersensitivity or idiosyncratic reactions but are in reality the effects of overdosage.

The use of ataractic drugs in the form of a "cocktail" in anaesthesia has been criticized during the past few years. It is the writer's opinion, and this is shared by many, that the new therapeutic agents should not be administered in combinations until precise knowledge of their actions, and wide experience in their use has determined the efficacy of each constituent. Advantage may be taken then of

combining these drugs for some more desirable effect. It must be recognized, however, that the toxicity of drugs is usually increased when they are used in combination (130). On the other hand, the combination of homeopathic doses of several drugs in order to provide broad action and to reduce the undesirable effects of the individual compounds results in an apparent reduction of their over-all efficacy. (131) Another action of many of these drugs to be considered is that they are capable of producing conditions such as allergy, while at the same time they are of value in the treatment of similar diseases (132, 133).

The many reports on the physiological and pharmacological responses to the ataractics are providing us with an insight into the specific effects of these agents on the heart and circulation, on the lungs and respiration, on the functions of the nervous system, and of other vital processes. These must be supplemented extensively in the immediate future

These agents now can assist us in approaching an ideal in anaesthesia in which the patient may be permitted to have a restful, undisturbed period of sleep the night before an operation provided by a hypnotic drug which has a moderately rapid onset of action, lasts 6-8 hours and has no "hangover" effects On the morning of operation, he may be rendered ataraxic for preoperative preparation. When all is ready, sedation, sub-hypnosis or deep sleep can be induced smoothly, without subjective discomfort and with minimal physiological disturbance The period of operation can be managed by appropriate drugs to maintain light hypnosis, and to provide sufficient analgesia, muscle relaxation and reflex suppression during the operation. Postoperatively, the effects of the hypnotic and muscle relaxant drugs may wear off promptly while light analgesia, ataraxia, and depression of the vomiting centre may persist for several hours, or until the acute disturbances caused by anaesthesia and surgical trauma have subsided.

This state of affairs would be ideal, if attainable By a careful selection from the wide array of drugs which are now available, this state can indeed be provided. The anaesthetist must learn to recognize anxiety and apprehension in his patients, even when these are not evident from overt behaviour or from changes in physiological parameters (pulse rate, blood pressure and character of breathing). He must then produce a controlled differential disintegration of the nervous system (134) that will prevent many of the serious endocrine and metabolic disturbances caused by anxiety and by anaesthesia which worried Wesley Bourne a generation ago, and have troubled all anaesthetists since; thus avoiding the inception of deleterious body changes in the period of surgical convalescence which are currently under extensive study by Francis Moore and many others (135-139) (see Fig. 2).

Anaesthetists occasionally "try" new drugs in clinical anaesthesia in an uncritical manner and without detailed knowledge of their pharmacology and of what to expect with human administration. On the other hand, there are those who stand pat with existing agents and hurl criticism at those who wish to employ the newer therapeutic drugs. There are two guiding rules which would be helpful to both groups. The first is the most honourable test of starting with yourself. One quickly learns the dose-response of a drug in this way. Osmond states that this test helps us as nothing else can to assess the value of verbal and published

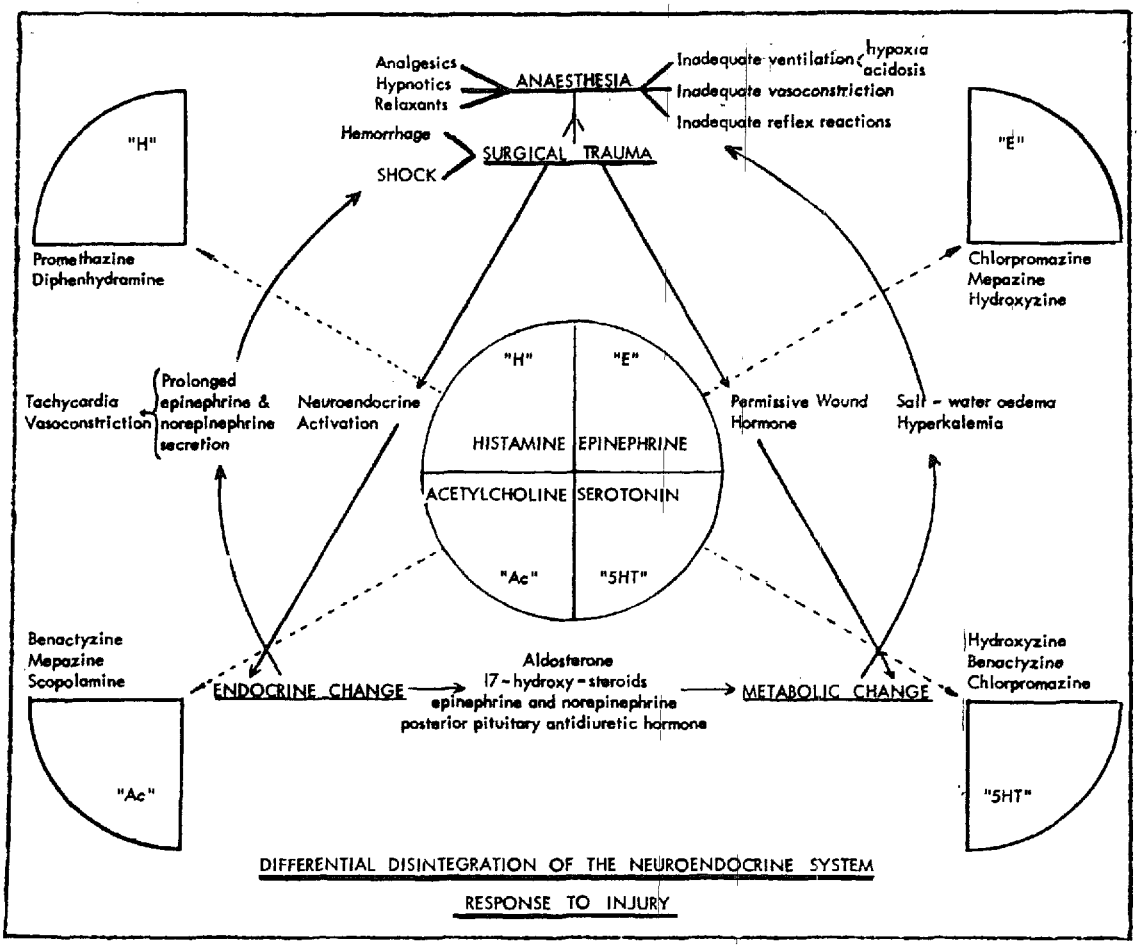


FIGURE 2. Schematic outline of manner in which ataractic drugs may block, under controlled conditions, the deleterious effects of anaesthesia and surgical trauma on the "normal" endocrine reactions which promote wound healing. The reactions usually observed after surgical trauma are: (*a*) corticosteroids are elevated in the blood; (*b*) *aldosterone production* is increased—and is elevated in the urine; (*c*) catecholamines are elevated in the blood; (*d*) antidiuresis occurs—patient cannot excrete water without solute.

reports and permits a more critical analysis of them (140). This method is especially useful with psychotherapeutic drugs. The second is that recommended by Noseworthy (141):

We should take every opportunity not only of watching others at work, but also of noting the subsequent condition of their patients. If we then honestly believe that our own results would have been the same, or better, well and good for the moment. If, on the other hand, we recognize that our own efforts do not stand up to such a comparison, three honourable courses are open to us: *aut disce*—either we can learn such techniques, perhaps even evolving something better; *aut discede*—or we can retire gracefully without regret or crabbed criticism; *maret sors tertial caedi*—there remains a third course, acknowledging our own shortcomings, we can help and encourage others —not to return, but to take stock and advance.

By following these recommendations, better insight into the role of ataractics in anaesthesia can be determined and their evaluation may be continued safely on a wide scale. The most reliable and valid way to evaluate these drugs further is to substitute them for the "routine" agents now in use, rather than to employ

them in conjunction with or as adjuvants to the older drugs. The experience accumulated during the next few years may then provide us with an objective and reliable assessment of them so that their efficacy, dangers and disadvantages may be classified

RÉSUMÉ

Au cours de la dernière décade, nous avons été témoins de l'apparition, avec grand succès d'ailleurs, de nombreux médicaments capables de modifier l'attitude des gens qui prennent ces médicaments Non seulement, ces médicaments peuvent faire disparaître l'excitation et l'anxiété, mais encore ils peuvent enrayer la dépression et rétablir la stabilité et l'imperturbabilité (2). Fabing a suggéré le mot "ataraxique" pour décrire ce changement d'attitude produit par des médicaments.

Pour l'anesthésiste qui entre en contact quotidien avec des malades qui ont, en même temps, des problèmes physiques de grande importance et un état psychique empreint d'une grande anxiété ou d'une profonde dépression, il devient très important qu'il voit clair dans cette affluence toujours croissante de médicaments pouvant influencer l'attitude de ceux qui les consomment. La connaissance de ces médicaments ne fera qu'en rendre l'emploi plus judicieux pour le bénéfice du malade et de l'anesthésiste. L'examen répété des épreuves cliniques et expérimentales de ces médicaments devrait constituer la seule base pour justifier leur emploi en clinique L'efficacité de chacune de ces drogues doit demeurer soumise à la connaissance précise de ses actions multiples et de ses principaux dangers, renseignements qui nous sont procurés par les expériences des autres (3, 4, 5).

En anesthésie, la première fonction des ataraxiques est de diminuer la tension nerveuse, très probablement en inhibant, dans la substance reticulée souscorticale, la transmission ou cortex d'influx nuisibles, moteurs sensitifs ou psychiques. Il est également possible qu'ils agissent en élevant le seuil da la réponse réflexe à une stimulation dans des zones spécifiques. le cortex, le thalamus, l'hypothalamus, la moelle épinière et certaines zones sensitives hautement réflexogènes de l'organisme (14). Ils procurent également un état de détente physique et psychique nécessaire à l'induction du "sommeil naturel". En conséquence, pour préciser quantitativement et qualitativement l'action de ces médicaments, nos efforts devraient tendre à procurer au clinicien une échelle pour l'évaluation des limites d'utilité de chacun des ataraxiques avec une mention spéciale de son pouvoir d'action sur le système nerveux autonome

Dans la Figure 1, on peut prendre connaissance des formules développées de chacun de ces composés. On a résumé dans la Table I. le nom commercial, l'efficacité en anesthésie, la dose moyenne pour la prémédication en anesthésie (chez les malades de 15 à 60 ans dont l'état de santé est de risque 1 ou 2) ainsi que les réactions importantes et les dangers.

Le renseignement essentiel à apporter à l'anesthésiste qui emploie ces médicaments doit concerner d'abord: la puissance du médicament, les limites d'action, ses effects sur les signes vitaux et la fréquence de ses réactions allergiques. Ces renseignements sont précieux pour décider de la dose dans une situation donnée. Ensuite, l'anesthésiste doit être renseigné sur la possibilité de la drogue en question à potentialiser les autres médicaments employés en anesthésie: sédatifs, hypnotiques, analgésiques ou myorésolutifs; en troisième lieu, il doit être

renseigné sur les modifications d'action possibles de chacun des médicaments car l'effet de certains médicaments n'offre qu'une marge étroite dans leur réponse tandis que la plupart des médicaments sont reconnus pour apporter une grande variété de réponses individuelles même chez les sujets en santé (129).

La connaissance de ces détails deviendra précieuse pour prédire si une dose donnée saura produire l'effet désiré ou donnera des réactions toxiques et des effets indésirables. Elle permettra également à l'anesthésiste d'éviter ce qu'on appelle fréquemment de l'hypersensibilité ou de l'idiosyncrasie, et qui n'est, en réalité, que le résultat d'un surdosage.

Au cours des dernières, années, on a critiqué ce qui se pratique en anesthésie: l'emploi des ataraxiques sous forme de "cocktail." C'est l'opinion de l'auteur, opinion qui est partagée d'ailleurs par un grand nombre, que les agents thérapeutiques ne devraient pas être employés en associations avant qu'une connaissance précise de leurs actions et une grande expérience de leur usage aient précisé l'efficacité de chacun des composants de l'association. C'est alors qu'il peut y avoir intérêt à associer ces médicaments pour accroître l'effet désireé. Il faut se rappeler, toutefois, que la toxicité des médicaments augmentent habituellement quand on les emploie en associations (130). Par contre, l'association de doses homéopathiques de différents médicaments, pour obtenir une action plus vaste et diminuer les effets nuisibles des divers composants, entraîne une diminution de l'efficacité totale (131). Il faut également retenir que plusieurs de ces médicaments possèdent un autre pouvoir: celui de provoquer des états comme l'allergie tout en possédant, en même temps, une certaine valeur pour lutter contre de semblables maladies (132, 133).

Les nombreux résultats d'études sur la physiologie et la pharmacologie des ataraxiques nous permettent de jeter un coup d'œil sur le mécanisme intime d'action et sur les effets spécifiques de ces agents sur le cœur et la circulation, sur les poumons et la respiration, sur les fonctions du système nerveux et sur les autres processus vitaux. Dans l'avenir, il faudrait accroître et étendre ces études

Ces drogues peuvent nous aider à atteindre un idéal en anesthésie, idéal qui consisterait à procurer, au malade qui doit être opéré le lendemain, une nuit complète et reposante en lui faisant absorber un hypnotique à action assez rapide, à durée d'action de 6–8 heures, ne possédant aucun effet indésirable. Le matin de l'opération, le malade pourrait être mis en état d'ataraxie pour la préparation préopératoire. Puis, quand tout serait prêt, on pourrait procurer soit une sédation, soit un sommeil léger, soit une sommeil profond avec un minimum d'ennuis personnels et de désordres physiologiques pour le malade. Durant l'opération, il audrait posséder un choix de médicament permettant de maintenir un sommeil léger, de procurer une analgésie suffisante, un relâchement musculaire convenable et la suppression des réflexes nuisibles. Après l'opération, il faudrait que les hypnotiques et les myorésolutifs soient métabolisés rapidement tandis que les effets des analgésiques, des ataraxiques et des dépresseurs du centre des vomissements se prolongent pendant plusieurs heures ou jusqu'à ce que cessent ou disparaissent les ennuis causés par l'anesthésie et le traumatisme chirurgical.

Voilà ce qui serait l'idéal, s'il est possible de l'atteindre. Actuellement, en faisant un choix judicieux des médicaments à notre disposition, il est possible de procurer cet état. L'anesthésiste doit apprendre à dépister, chez ses malades,

l'anxiété et l'appréhension, même si elles sont masquées par de la fanfaronnade en s'aidant des modifications physiologiques (rythme cardiaque, tension artérielle et le type de respiration) C'est alors que l'anesthésiste doit exécuter une dissociation différentielle du système nerveux du malade (134) qui pourra prévenir de sérieux troubles métaboliques et endocriniens causés par l'anxiété et l'anesthésie, ce qui inquiétait Wesley Bourne il y a une génération et qui n'a cessé de laisser perplexes tous les anesthésistes depuis ce temps On évitera ainsi l'installation du changements nuisibles dans l'organisme au moment de la convalescence chirurgicale, changements qui font l'objet d'une étude extensive par Francis Moore et d'autres (135–139) (voir fig 2)

Il y a des anesthésistes qui, à l'occasion, emploient des nouveaux médicaments en anesthésie clinique et, cela, sans esprit critique, sans connaissance précise de leur pharmacologie et sans expectative précise de leur administration à l'homme Par contre, il y en a d'autres qui suivent les sentiers battus avec les agents connus et ne craignent pas d'adresser des critiques à ceux qui désirent employer des médicaments plus nouveaux. Il y a deux lignes de conduite qui pourraient être utiles aux deux groupes la première est l'épreuve la plus honorable: faire la première épreuve sur eux-mêmes De cette façon, un individu apprend rapidement la dose-réponse d'une drogue. Osmond affirme que cette épreuve est plus précieuse qu'aucune autre pour apprécier la valeur des résultats verbaux et publiés sur le sujet et que cela en permet en même temps une analyse plus critique (140) La seconde ligne de conduite est dictée par Nosworthy (141).

> Nous ne devrions pas manquer une occasion de regarder travailler les autres, mais aussi de suivre l'évolution de leurs malades Si, en toute honnêteté, nous avons la conviction que nos résultats auraient été les mêmes, ou meilleurs, à la bonne heure pour le moment Si, par contre, nous réalisons que nos efforts ne supportent pas une semblable comparaison, il y a trois issues honorables qui s'offrent à nous *aut disce* — ou nous pouvons apprendre ces techniques et peut-être en réaliser des meilleures, *aut discede* —ou nous pouvons abandonner, avec grâce, sans regret ni critique, *maret sors tertial caedi* — il reste une troisième issue tout en reconnaissant notre insuccès, nous pouvons aider et encourager les autres — non pas à reculer mais à s'armer et à avancer

En suivant ces conseils, nous obtiendrons une meilleure connaissance du rôle des ataraxiques en anesthésie et nous pourrons en continuer, en toute sécurité et sur une haute échelle, les applications cliniques. La façon la plus certaine et la plus objective d'étudier ces médicaments est de les substituer aux agents de "routine" dans le moment plutôt que de les associer ou de s'en servir comme adjuvants aux anciens médicaments. L'expérience que nous acquérerons durant les années à venir peut nous apporter des arguments fiables et objectifs et nous permettre d'en préciser l'efficacité, les dangers et les désavantages

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