SEDATIVES, ANALGESICS, ANTIDOTES, AND THEIR INTERACTION A REVIEW

ALLEN B DOBKIN, M D *

THE ANAESTHETIST is harassed constantly by three needs in his daily work Each of these contributes to the things that make the difference between an "uneventful anaesthetic" and one charged with complications They are related in part to our desire for drugs with special properties which can produce in the patient a certain response without any deleterious or other undesirable effect, and can be listed as follows

1 Sedatives which produce effective psychic sedation during the immediate preoperative period, without provoking nausea, vomiting, severe respiratory depression, circulatory instability, histamine-like reactions, and behavioural disturbances [1]

2 Potent analgesics, with a relatively short delay in onset and a short duration of action, that do not cause side-effects as noted above [2 3] Skeletal muscle relaxation and deep hypnosis (unconsciousness) are not necessary features of the action of these agents, since we have suitable relaxant drugs, and deep hypnosis or unconsciousness can be well provided by nitrous oxide [4]

3 Antidotes which can ensure rapid, smooth recovery to wakefulness and adequate breathing, without provoking nausea, vomiting, sneezing, coughing, itching, or circulatory disturbances These drugs should only be used when clearly indicated [5]

PSYCHIC SEDATION

The introduction of drugs which are capable of producing tranquillity was a mixed blessing to the anaesthetist During the past decade, we have realized that analgesics and hypnotics alone (or in combination) do not always satisfy the desire to sedate a patient In the search for better sedatives, many new drugs have been tested to see if one meets this real need, but better ones must still be sought, and their actions compared with those already in use A summary of these structurally is shown in Table I Selection of the best one among these to fit our needs has been hampered by the wide dose range of the drugs within particular chemical groups, and by variable side-effects that occur with individual representatives of each group of drugs, as indicated in Table I

None of the drugs is a "perfect" sedative in the sense that it will invariably induce a state of calm indifference to a major stress situation, even when the dose is increased to the range where toxic effects are seen too frequently (>25%) Aldous Huxley has stated that

> the perfect tranquilizer should be a drug which would relieve and console our suffering species without doing more harm in the long run than it does good in the short It must be less likely to produce undesirable social consequences than alcohol or barbiturates, less inimical to the heart and lungs than the tar and nicotine of cigarettes It should

*Professor and Chairman, Department of Anesthesiology, State University of New York, Upstate Medical Center, Syracuse 13210, New York

produce changes in consciousness more pleasant and more intrinsically valuable than mere hypnotic sedation or dreaminess, delusions of omnipotence or release from inhibition

This is still a fantasy, and applies, of course, to drugs that will be used over a protracted period of time

There are divergent opinions regarding the use of sedative drugs in premedication Some feel that none should be used—particularly narcotic analgesics[6] and non-barbiturate sedatives[7]—while others like to use enough to "obtund, obnubilate and obfuscate"[8] Beecher has asserted that there is no place for analgesics in premedication unless the patient has pain, mainly because a true sedative action is only evident when pain is relieved Otherwise nausea, itchiness, and respiratory depression become their most prominent effects Many dislike the barbiturates because they cause confusional states, especially in the elderly, in whom a sensation of unreality accompanies the induced half-asleep state, which increases the alarm caused by an unfamiliar environment Psychosedatives are feared because they may cause or augment depression of circulation and respiration Neurosedatives are not widely used because most of them must be given over a period of several days before an adequate sedative effect becomes apparent

The use of psycho- and neuro-sedatives in psychiatric practice is rather different from that in anaesthesia because the type of anxiety that appears in the psychotic patient has no obvious purpose, yet requires long therapy with large doses to allay the patient's symptoms, whereas the preoperative patient usually has good reason to be anxious and even better reasons to be rendered tranquil in a relatively short time This *can* be accomplished by judicious use of psychosedatives and is ample reason for us to continue studying these drugs carefully, and to persist in our quest for drugs that can consistently allay a patient's fears after a single injection

Even more important to the anaesthetist than being able to provide a highly consistent sedative effect with a drug is the requirement for a lack of undesirable physiological disturbances, such as hypotension (especially in the hypertensive patient), respiratory depression (particularly in the patient with emphysema), extrapyramidal effects ("twitchiness," restlessness, muscle spasms), and allergic-type reactions Some of the undesirable responses to sedative and analgesic drugs in the ill patient are shown in Table II

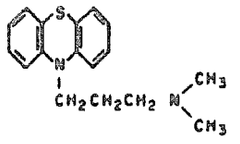
Nodine and his associates have discussed the human bio-assay of psychosedative drugs and have suggested that when the efficacy of these drugs is studied, the percentage of patients showing moderate to marked improvement should be plotted against the logarithm of the dose[9] At any low dose level, 30 to 40 per cent of patients may be expected to respond because of a placebo effect As the dose is increased, a higher percentage of patients should respond until a maximum is reached, leaving only a few patients who do not respond adequately to the drug The incidence of toxic effects should be plotted in the same way, defining a toxic effect as one which is sufficiently severe in the patient and alarming to the physician that administration of the drug is discontinued or the dose is lowered Figures 1A and 1B show the typical response that may be expected from a satisfactory and an unsatisfactory sedative drug

TABLE I

SUMMARY OF DRUGS WITH SEDATIVE PROPERTIES SHOWING THE AVERAGE DOSE, PRIMARY TYPES OF SEDATION, OTHER MAJOR EFFECTS, UNDESIRABLE SIDE-EFFECTS, AND THEIR EFFICACY IN ANAESTHESIA PRACTICE

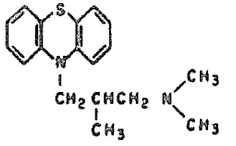
Neuro & Hypno & Psycho Sedatives

PROMAZINE — Sparine



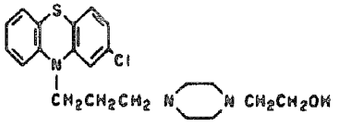
1 50 MG (P)
2 HS NS SD
3 P R BP BT AM AE
4 EX AL RES
5 1 2

TRIMEPRAZINE — Temaril, Alimemazine



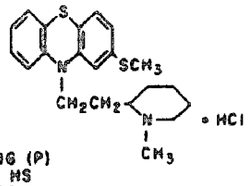
1 5 MG (P)
2 HS SD
3 P R BP AM AS AH (ANTIPRURITIC)
4 –
5 1

PERPHENAZINE — Trilafon



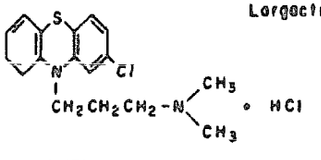
1 5 MG (P)
2 NS HS
3 BP AM AR
4 EX AL RES
5 1 (ANTIEMETIC)

THIORIDAZINE — Melleril



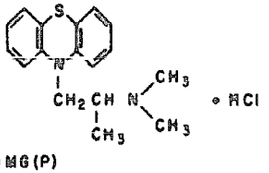
1 5 MG (P)
2 NS HS
3 P BP
4 EX AL RES
5 2

CHLORPROMAZINE — Thorazine, Largactil



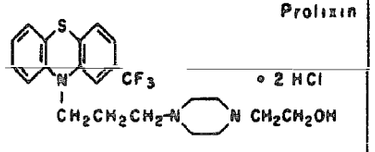
1 25 MG (P)
2 HS NS PS SD
3 P R BP BT AM AR AS AE AHT
4 AL ME RES
5 1 2

PROMETHAZINE — Phenergan



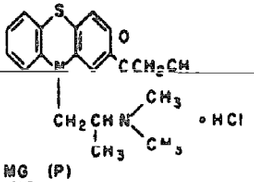
1 50 MG (P)
2 HS
3 P R AM AS AH
4 RES
5 1-2

FLUPHENAZINE — Trancin, Prolixin



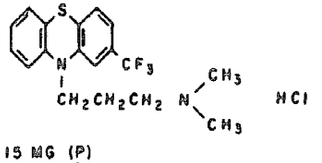
1 4 MG (P)
2 HS NS
3 P BP AM AS AE
4 EX AL RES
5 1 (ANTIEMETIC)

PROPRIOMAZINE — Largon



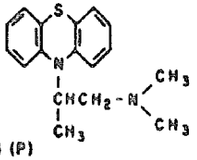
1 20 MG (P)
2 HS NS
3 P R BP AM AS AE AH
4 EX RES
5 1-2

TRIFLUOPROMAZINE — Vesprin



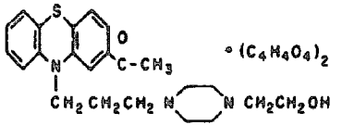
1 15 MG (P)
2 HS NS PS
3 P R BP BT AM AR AE AHT
4 EX AL ME RES
5 1 2

ISOPROMETHAZINE — WIN 10 409



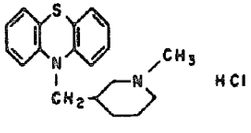
1 50 MG (P)
2 HS
3 P AM AH
4 ?
5 ?

ACETOPHENAZINE — Tindal



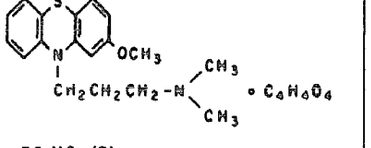
1 20 MG (P)
2 NS HS PS
3 BP
4 EX AL RES
5 2 3

MEPAZINE — Pacatal



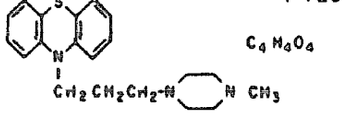
1 75 MG (P)
2 NS
3 BP AR AS AE AC
4 AL
5 2

METHOXYPROMAZINE — Tentone



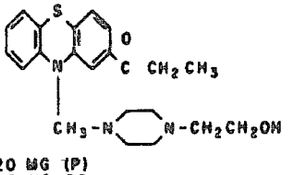
1 30 MG (P)
2 NS
3 BP
4 AL
5 2 3

PERAZINE — Taxilan, P 725



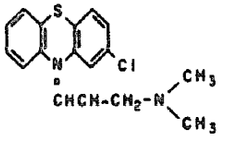
1 50 MG (P)
2 NS
3 ?
4 ?
5 ?

CARPHENAZINE — Proketazine



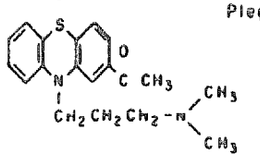
1 20 MG (P)
2 NS HS PS
3 –
4 EX
5 2 3

CHLORPROTHIXENE — Taractan



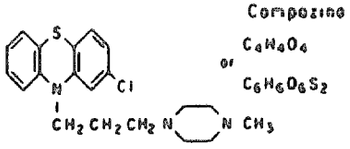
1 10 MG (P)
2 HS NS
3 P R BP BT AM AE AC AHT
4 ?
5 2

ACEPROMAZINE — Notensil, Plegicil



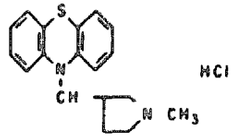
1 25 MG (P)
2 NS PS
3 P R BP BT AM
4 EX AL RES
5 2 3

PROCLORPERAZINE — Stemetil, Compazine



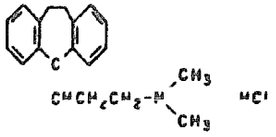
1 5 MG (P)
2 NS HS
3 P BP AM AS
4 EX AL RES
5 1 (ANTIEMETIC)

METHDILAZINE — Tacaryl



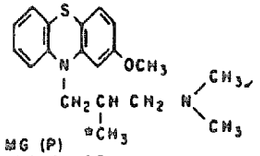
1 10 MG (P)
2 NS
3 P BP AM AS AH
4 ?
5 1 (ANTIHISTAMINIC)

AMITRIPTYLINE — Elavil



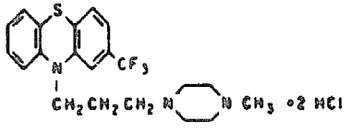
1 20 MG (P)
2 NS
3 P BP AC
4 EX AL RES
5 2

METHOTRIMEPRAZINE — Veractil
LEVOMEPROMAZINE — Nozinan



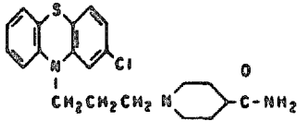
1 10 MG (P)
2 HS NS PS SD
3 P R BP BT AM AR AS AE AH AHT
4 AL
5 1

TRIFLUOPERAZINE — Stelazine



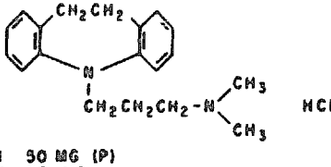
1 2 MG (P)
2 NS
3 AS
4 EX AL RES
5 2 3

PIPAMAZINE — Mornidine



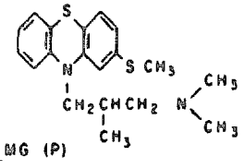
1 5 MG (P)
2 NS
3 AM AS AC
4 -
5 2 (ANTIEMETIC)

IMIPRAMINE — Tofranil



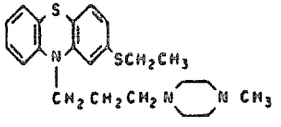
1 50 MG (P)
2 NS HS
3 P BP AC
4 EX AL RES ME
5 2

METHIOMEPRAZINE — Ventac, RP 7238



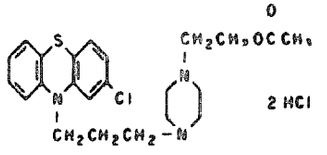
1 10 MG (P)
2 NS
3 ?
4 ?
5 ?

THIETHYLPERAZINE — Torecan



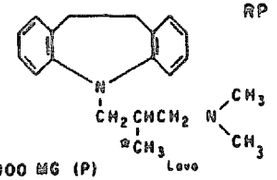
1 10 MG (P)
2 NS
3 P AM AE
4 -
5 1 (ANTIEMETIC)

THIOPROPAZATE — Dartal



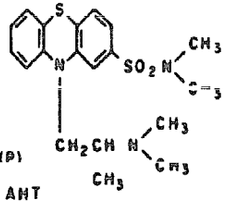
1 4 MG (P)
2 NS HS
3 AM AS AC
4 -
5 2 (ANTICHOLINERGIC)

TRIMEPRAMINE — Surmontil, RP 7162



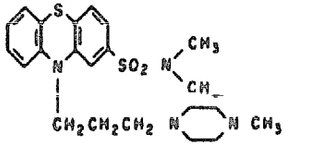
1 100 MG (P)
2 NS
3 P BP BT AM AS AH
4 EX
5 2

THIOPROMETHAZINE — RP 8599



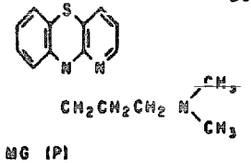
1 50 MG (P)
2 NS
3 AM AH AHT
4 ?
5 MIGRAINE

THIOPROPERAZINE — Majeptil



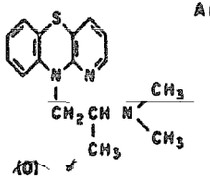
1 5 MG (P) 2 CH_3SO_3H
2 NS (WEAK)
3 P R AM
4 EX RES
5 1 2 (ANTIEMETIC)

PROTHIPENDYL — Timovan, Dominal



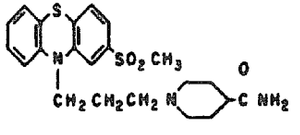
1 10 MG (P)
2 NS HS PS
3 P R BP AM AH
4 -
5 1 2

ISOTHIPENDYL — Theruhistin, Andantol



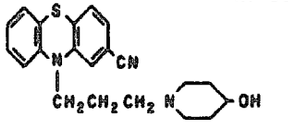
1 5 MG (O)
2 HS
3 AH
4 NE
5 2 (ANTIHISTAMINIC)

THIOPIPAMAZINE — RP 9965



1 15 MG (P)
2 NS
3 BP AM AE
4 ?
5 (ANTIEMETIC)

PROPERICIAZIN — Neuleptil, RP 8909



1 10 MG (P)
2 NS
3 P BP AM AE AC AHT
4 -
5 1 (ANTIEMETIC)

1 Dose (O) oral (P) parenteral

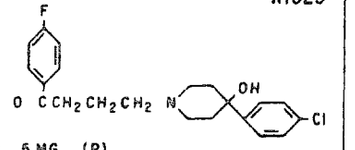
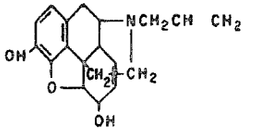
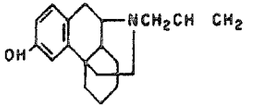
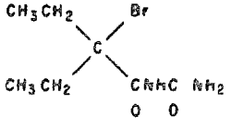
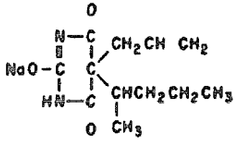
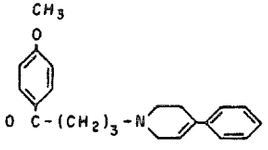
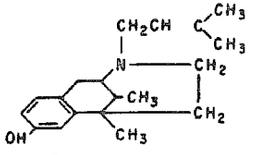
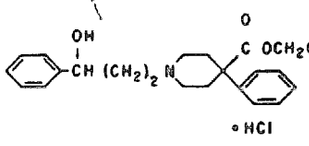
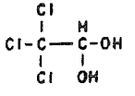
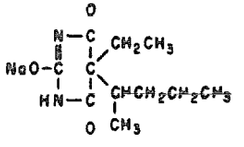
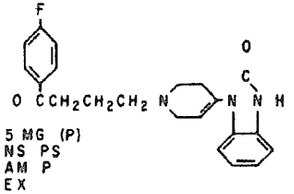
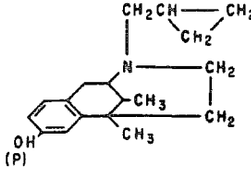
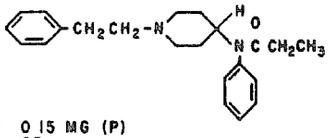
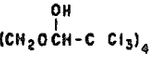
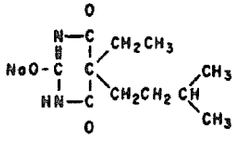
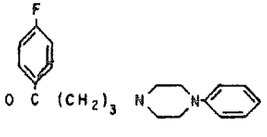
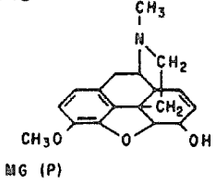
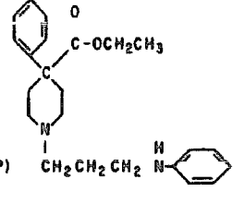
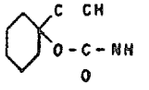
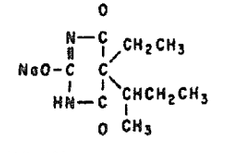
2 Type of Sedation
- HS hypnotic
- NS neurosedative
- PS psychosedative
- SD sensory deprivation
- MD motor deprivation

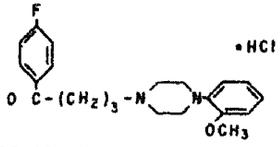
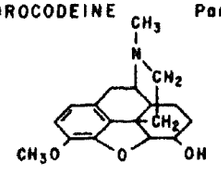
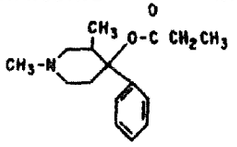
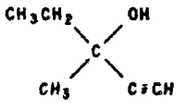
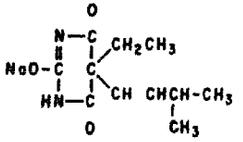
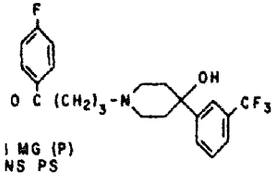
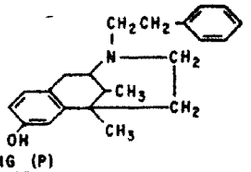
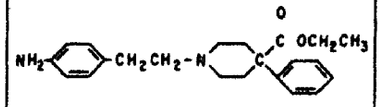
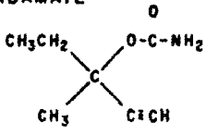
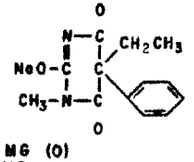
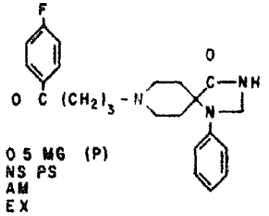
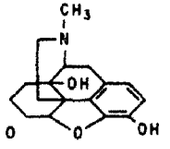
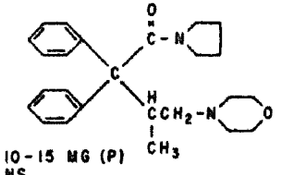
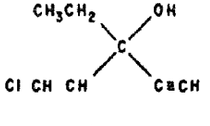
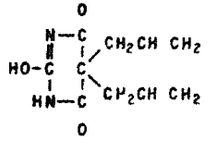
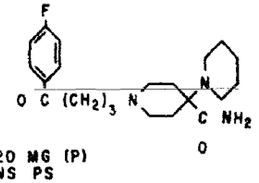
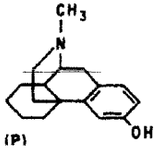
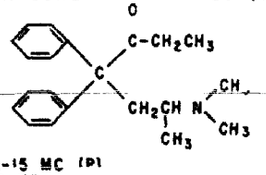
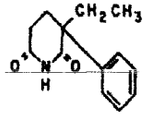
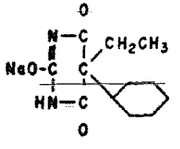
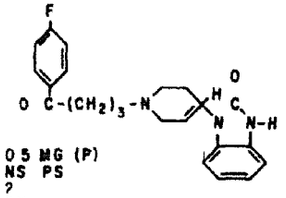
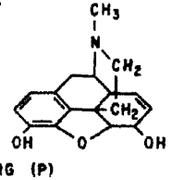
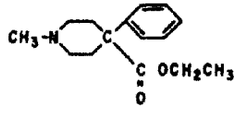
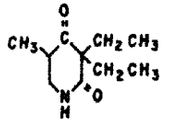
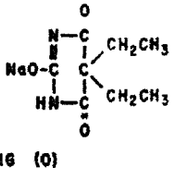
3 Other Effects
- P prolong anesthesia
- R respiratory depression
- BP hypotension
- BT hypothermia
- AM antiemetic
- AR antiarrhythmic
- AS antisialogogue
- AE antiepinephrine
- AC anticholinergic (antiacetylcholine)
- AH antihistaminic
- AHT antiserotonin (5 HT)

4 Side Effects
- NE nausea retching, vomiting
- EX neuromuscular disturbance extrapyramidal syndrome seizures
- AL allergy jaundice Bd dyscrasias skin disorders
- ME metabolic or endocrine upsets
- RES behavioral disturbances restlessness hallucinations
- AD addicting properties
- H histamine reactions

5 Efficacy
- 1 good
- 2 fair
- 3 poor

Sensory Deprivation & Hypnotic Sedatives

HALOPERIDOL Serenase R1625  1 5 MG (P) 2 NS PS 3 AM P BT R 4 EX (SEVERE) 5 3	**NALORPHINE** Nalline  1 10 MG (IV) 2 SD 3 R 4 RES 5 1 (REVERSE NARCOTIC DEPRESSION)	**LEVALLORPHAN** Lorfan  1 2 MG (IV) 2 SD 3 R 4 RES 5 1 (REVERSE NARCOTIC DEPRESSION)	**CARBROMAL**  1 1 GM (O) 2 HS 3 – 4 – 5 1	**SECOBARBITAL** Seconal  1 100 MG (O P) 2 HS 3 – 4 – 5 1-2
ANISOPERIDINE R 1647  1 50 MG (P) 2 NS PS 3 AM 4 EX 5 2 3	**PENTAZOCINE** WIN 20228  1 50 MG (P) 2 SD NS 3 R 4 ? 5 1 (ANALGESIA)	**PHENOPERIDINE** R 1406  2 SD NS 3 – 4 R EX NE 5 ?	**CHLORAL HYDRATE**  2 HS 3 – 4 – 5 1	**PENTOBARBITAL** Nembutal  1 150 MG (O P) 2 HS 3 – 4 RES AD 5 1
DEHYDROBENZPERIDOL R 4749 **DROPERIDOL** Inapsine  1 5 MG (P) 2 NS PS 3 AM P 4 EX 5 1	**CYCLAZOCINE** WIN 20 740  1 2 MG (P) 2 SD 3 ? 4 RES 5 ?	**FENTANYL** Sublimaze R 4263  1 0 15 MG (P) 2 SD 3 – 4 R NE EX (MUSCLE RIGIDITY) 5 1	**PETRICHLORAL** Pericior  1 1 GM (O) 2 HS 3 – 4 – 5 –	**AMOBARBITAL** Amytal  1 200 MG (O P) 2 HS 3 – 4 – 5 1
BUTROPIPAZONE R 1892  1 100 MG (P) 2 NS PS 3 AM 4 EX 5 2	**CODEINE**  1 60 MG (P) 2 SD 3 – 4 R NE AD(MILD) 5 1 2	**PIMINODINE** Alvodine  1 10 MG (P) 2 SD NS 3 – 4 R AD 5 1	**ETHINAMATE** Valmid  1 500 MG (O) 2 HS 3 – 4 – 5 2	**BUTABARBITAL** Butisol  1 100 MG (O) 2 NS HS 3 P 4 AD 5 2

HALOANISONE R 2167  1 25 MG (P) 2 NS PS 3 AM 4 EX 5 2 3	**DIHYDROCODEINE** Paracodin  1 30 60 MG (P) 2 SD 3 – 4 R NE AD (MILD) 5 1-2	**ALPHAPRODINE** Nisentil  1 60 MG (P) 2 SD NS 3 – 4 R NE AD 5 1	**METHYL PARAFYNOL** Dormison  1 500 MG (O) 2 HS 3 – 4 – 5 1	**VINABARBITAL** Delvinal  1 200 MG (O) 2 NS HS 3 – 4 AD 5 1-2
TRIPERIDOL R 2498  1 1 MG (P) 2 NS PS 3 AM BT P 4 EX 5 2	**PHENAZOCINE** Prinadol  1 3 MG (P) 2 NS SD 3 BP 4 R NE AD 5 1	**ANILERIDINE** Leritine  1 50 MG (P) 2 SD 3 – 4 NE R AD 5 1	**METHYLPENTYNOL CARBAMATE** Oblivon-C  1 200 MG (O) 2 HS 3 – 4 – 5 1	**MEPHOBARBITAL** Mebaral  1 100 MG (O) 2 NS MD 3 – 4 – 5 EPILEPSY
SPIROPERIDOL R 5147  1 0 5 MG (P) 2 NS PS 3 AM 4 EX 5 2	**OXYMORPHONE** Numorphan  1 1-1 5 MG (P) 2 SD NS 3 – 4 R NE AD? 5 1	**DEXTROMORAMIDE** Palfium  1 10-15 MG (P) 2 NS 3 – 4 R NE AD? 5 1	**ETHCHLORVYNOL** Placidyl  1 500 MG (O) 2 NS HS 3 – 4 – 5 1	**ALLOBARBITAL** Dial  1 150 MG (O) 2 NS HS 3 – 4 RES AD 5 2
DIPIPERON R 3345  1 20 MG (P) 2 NS PS 3 P BP AM 4 EX 5 2	**LEVORPHANOL TARTRATE** Levodromoran Levorphan  1 2 MG (P) 2 SD NS 3 – 4 R NE AD 5 1	**METHADONE** Dolophine  1 10-15 MG (P) 2 SD NS 3 – 4 R NE AD 5 1	**GLUTETHIMIDE** Doriden  1 500 MG (O) 2 HS NS 3 – 4 AD 5 1	**PHENOBARBITAL** Luminal  1 100 MG (O P) 2 HS 3 – 4 RES AD 5 2
BENZPERIDOL R 4584  1 0 5 MG (P) 2 NS PS 3 ? 4 EX 5 ?	**MORPHINE**  1 10-15 MG (P) 2 SD NS 3 – 4 R NE AD 5 1	**MEPERIDINE** Demerol  1 100 MG (P) 2 SD NS 3 – 4 R NE AD 5 1	**METHYPRYLON** Noludar  1 300 MG (O) 2 HS 3 – 4 – 5 1-2	**BARBITAL** Veronal Medinal  1 300 MG (O) 2 HS 3 – 4 RES AD 5 3

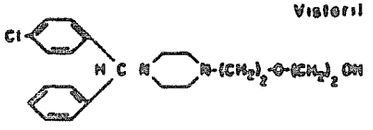
SUMMARY OF DRUGS WITH SEDATIVE PROPERTIES SHOWING GENERIC AND TRADE NAMES AND STRUCTURAL FORMULA NUMBERS UNDER EACH DRUG MEAN

1 AVERAGE DOSE
2 MAIN TYPES OF SEDATION
3 OTHER MAJOR EFFECTS
4 UNDESIRABLE SIDE EFFECTS
5 ANESTHETIC EFFICACY

ABBREVIATIONS ARE EXPLAINED AT BOTTOM LEFT OF CHART

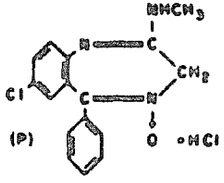
Neuro Sedatives

HYDROXYZINE — Atarax, Vistaril



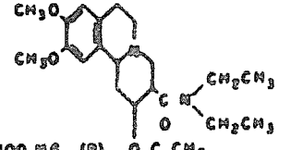
1 50 MG (P)
2 NS HS
3 P BP AHT AE AM
4 -
5 1

CHLORDIAZEPOXIDE — Librium
METHAMINODIAZEPOXIDE



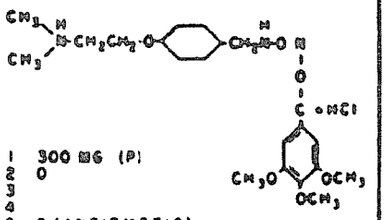
1 100 MG (P)
2 NS HS
3 P
4 -
5 1

BENZQUINAMIDE — Quantril



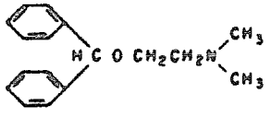
1 100 MG (P)
2 NS
3 -
4 -
5 -

TRIMETHOBENZAMIDE — Tigan



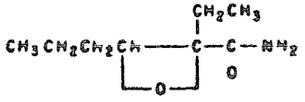
1 300 MG (P)
2 0
3
4
5 2 (ANTIEMETIC)

DIPHENHYDRAMINE — Benadryl



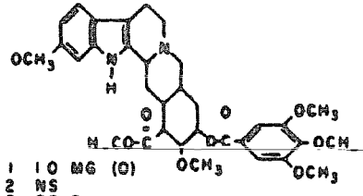
1 50 MG (P)
2 HS
3 AH P AS
4 -
5 1

OXANAMIDE — Quiactin



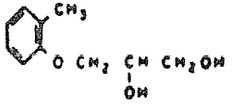
1 600 MG (O)
2 NS MD
3 -
4 -
5 3

RESERPINE — Serpasil



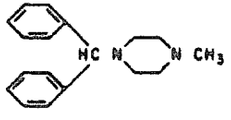
1 10 MG (O)
2 NS
3 BP P
4 EX ME AL
5 3

MEPHENESIN — Myanesin



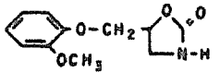
1 1 GM (O P)
2 NS MD
3 -
4 -
5 3

CYCLIZINE — Marezine



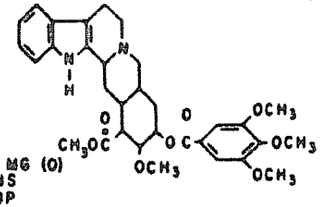
1 50 MG (P)
2 HS
3 AH AM
4 -
5 1 (ANTIEMETIC)

MEPHENOXALONE — Trepidone



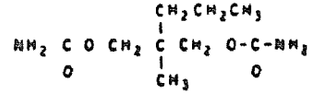
1 800 MG (O)
2 NS
3 -
4 -
5 3

DESERPIDINE — Harmonyl



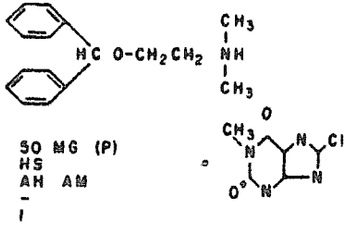
1 1 MG (O)
2 NS
3 BP
4 -
5 3

MEPROBAMATE — Miltown



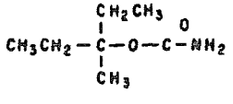
1 800 MG (O)
2 NS MD
3 -
4 AL AD
5 2 3

DIMENHYDRINATE — Gravol, Dramamine



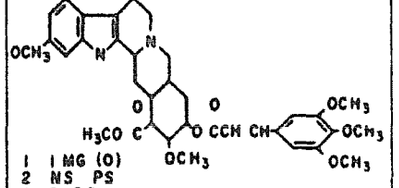
1 50 MG (P)
2 HS
3 AH AM
4 -
5 1

EMYLCAMATE — Striatran



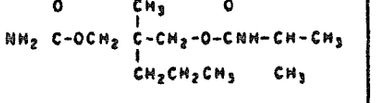
1 400 MG (O)
2 NS MD
3 -
4 -
5 2 3

RESCINNAMINE — Moderil



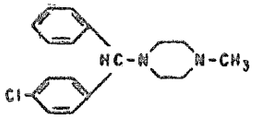
1 1 MG (O)
2 NS PS
3 P BP
4 RES EX
5 3 (TOO SLOW)

CARISOPRODOL — Soma, Rela



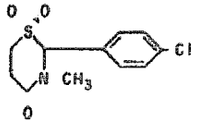
1 350 MG (O)
2 MD NS
3 -
4 AL
5 ?

CHLORCYCLIZINE — Diparalene



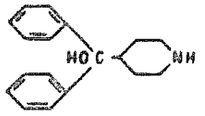
1 50 MG (O)
2 NS
3 AS AH
4 –
5 2 3

CHLORMETHAZANONE — Trancopal



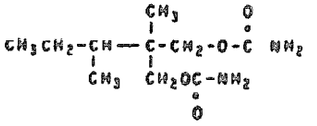
1 150 MG (O)
2 NS MD
3 –
4 AL NE
5 2

AZACYCLONOL — Frenquel



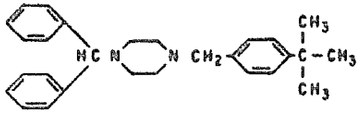
1 10 MG (P)
2 PS NS MD
3 AHT
4 –
5 1 (ACUTE MANIA)

MEBUTAMATE — Capla



1 300 MG (O)
2 NS
3 BP
4 ?
5 ?

BUCLIZINE — Softran

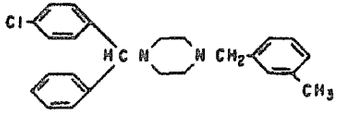


1 100 MG (O)
2 NS
3 P AH
4 NE
5 2-3

ECTYLUREA — Nostyn

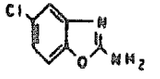
1 600 MG (O)
2 NS
3 –
4 –
5 3

MECLIZINE — Bonamine



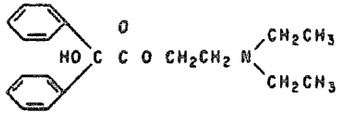
1 50 MG (O)
2 NS
3 AM
4 –
5 2 (ANTIEMETIC)

ZOXOZOLAMINE — Flexin



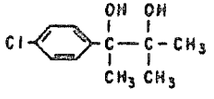
1 500 MG (O)
2 MD
3 –
4 OFF MARKET - TOO TOXIC
5 3

BENACTYZINE — Suavitil



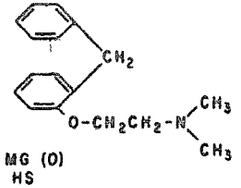
1 2 MG (O)
2 NS MD
3 P AC AHT AS
4 –
5 2

PHENAGLYCODOL — Acalo



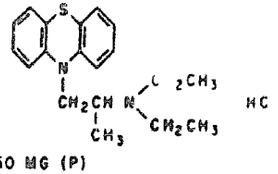
1 600 MG (O)
2 NS
3 –
4 –
5 3

PHENYLTOLOXAMINE — PRN



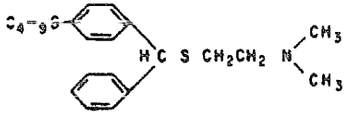
1 50 MG (O)
2 NS HS
3 AH
4 –
5 3

ETHOPROPAZINE — Parsitan



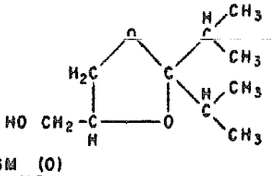
1 50 MG (P)
2 MD NS
3 –
4 EX
5 –

CAPTODIAMINE — Suvren



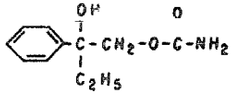
1 300 MG (O)
2 NS MD
3 P
4 –
5 2 3

PROMOXOLANE — Dimethylane



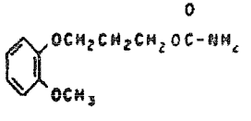
1 1 GM (O)
2 NS MD
3 ?
4 ?
5 3

HYDROXYPHENAMATE — Listica



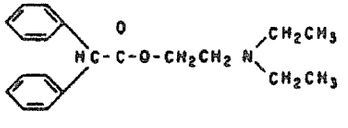
1 200 MG (O)
2 NS
3 –
4 –
5 –

METHOCARBOMAL — Robaxin



1 1 GM (O)
2 MD
3 –
4 NE AL
5 1-2

ADIPHENINE — Trasentine



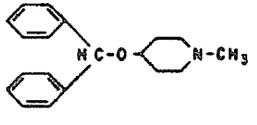
1 50 MG (O)
2 NS (ANTISPASMODIC)
3 AC AS
4 –
5 2

ETHANOL — Alcohol

CH_3CH_2OH

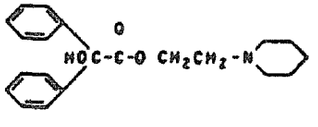
1 50 GM (O P)
2 NS
3 –
4 EX RES AD
5 1 2

DIPHENYLPYRALINE — Diafen



1 2 MG (O)
2 –
3 AH
4 –
5 ANTIHISTAMINE

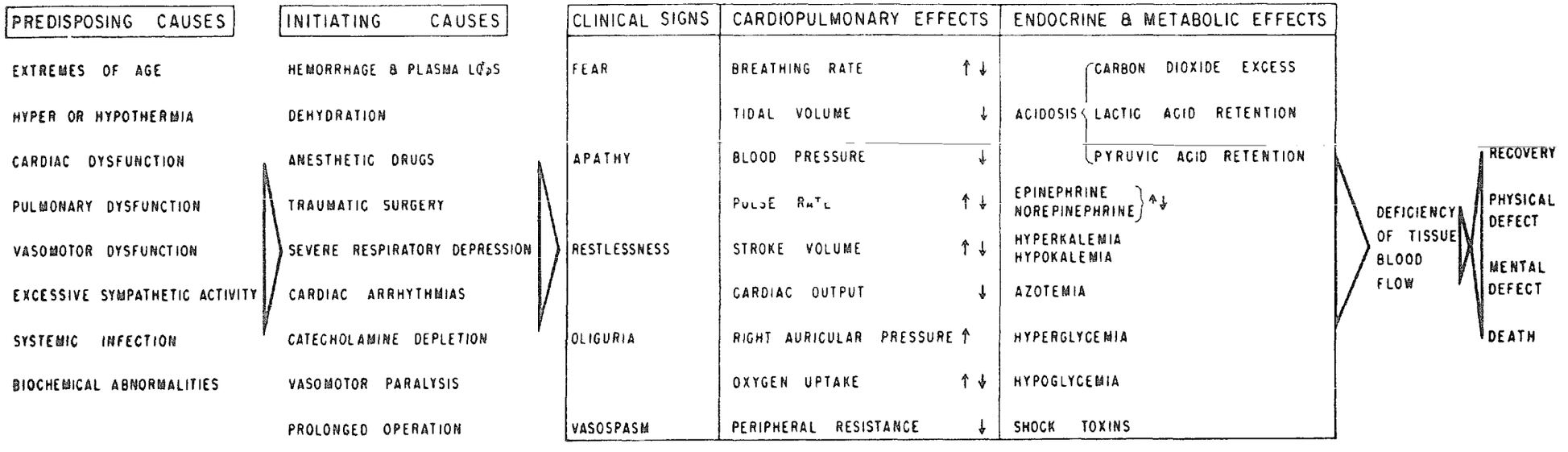
PIPERILATE PIPETHANATE — Sycotrol



1 2 MG (O)
2 NS MD
3 –
4 –
5 ?

TABLE II

PRIMARY FACTORS AFFECTING RESPONSE OF ILL PATIENTS TO SEDATIVE AND ANALGESIC DRUGS



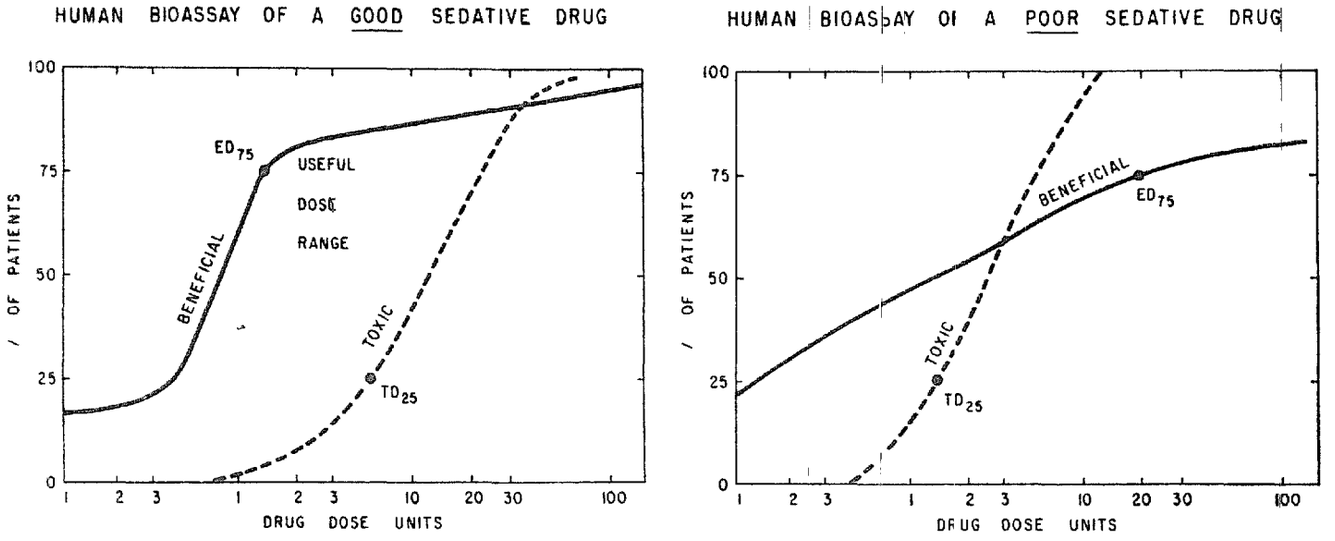


FIGURE 1 Human bioassay of a good (A) and a poor (B) sedative drug Observe that a drug should be effective in at least 75 per cent of patients (ED_{75}) at a dose level that does not cause toxic effects in more than 25 per cent of patients (TD_{25}) Otherwise the drug must be considered unsuitable as a sedative In anaesthetic practice, we should use only those drugs with a very wide therapeutic index (TD_{25} should be three times greater than ED_{75}).

Since psychosedative drugs are seldom used more than once in a patient in association with a single anaesthetic, it is reasonable to expect that the therapeutic effectiveness should be at least 95 per cent without appreciable toxic effects, and the "best" dose of the drug should be *no more* than one third of the dose which causes toxic effects in 25 per cent of patients If a toxic effect does develop, there should always be another drug available which effectively and promptly relieves the toxicity, and which itself should be virtually 100 per cent non-toxic in the therapeutic dose range

Hebb believes that the nervous system produces spontaneous activity and it requires outside stimulation to use up the energy produced He has suggested that the "cue response" and the intensity of arousal of the central nervous system are separate functions [10] Many of the drugs used in association with anaesthesia may be fitted into a bell-shaped curve, the abscissa of which corresponds to the intensity of arousal activity and represents non-specific nervous stimulation, and the ordinate of which corresponds to the cue value of a stimulus which represents well-organized, goal-directed behaviour (Fig 2)

Most of the available phenothiazine-related psychosedatives are shown in the central section of this figure I have placed them in this central position because they affect the psychomotor system in different ways, depending on their chemical side-chain structure and upon the psychic state of the subject They can not only suppress severe agitation and reduce a manic patient to a placid state, but they can sometimes cause wide mood swings in the relatively normal individual —from a state of indifference and drowsiness to one of panic and catatonia On the other hand, the patient who is weak and ill from a physical ailment is easily put to sleep, and, with excess, may go into coma, for these drugs have a potent depressant effect on the brain stem arousal mechanism [11]

The usual response in the "normal" subject to a psychosedative may be expected to vary from a mild hypnotic reaction—which merely depresses the cerebral cortex and raises the threshold of the central nervous system, causing

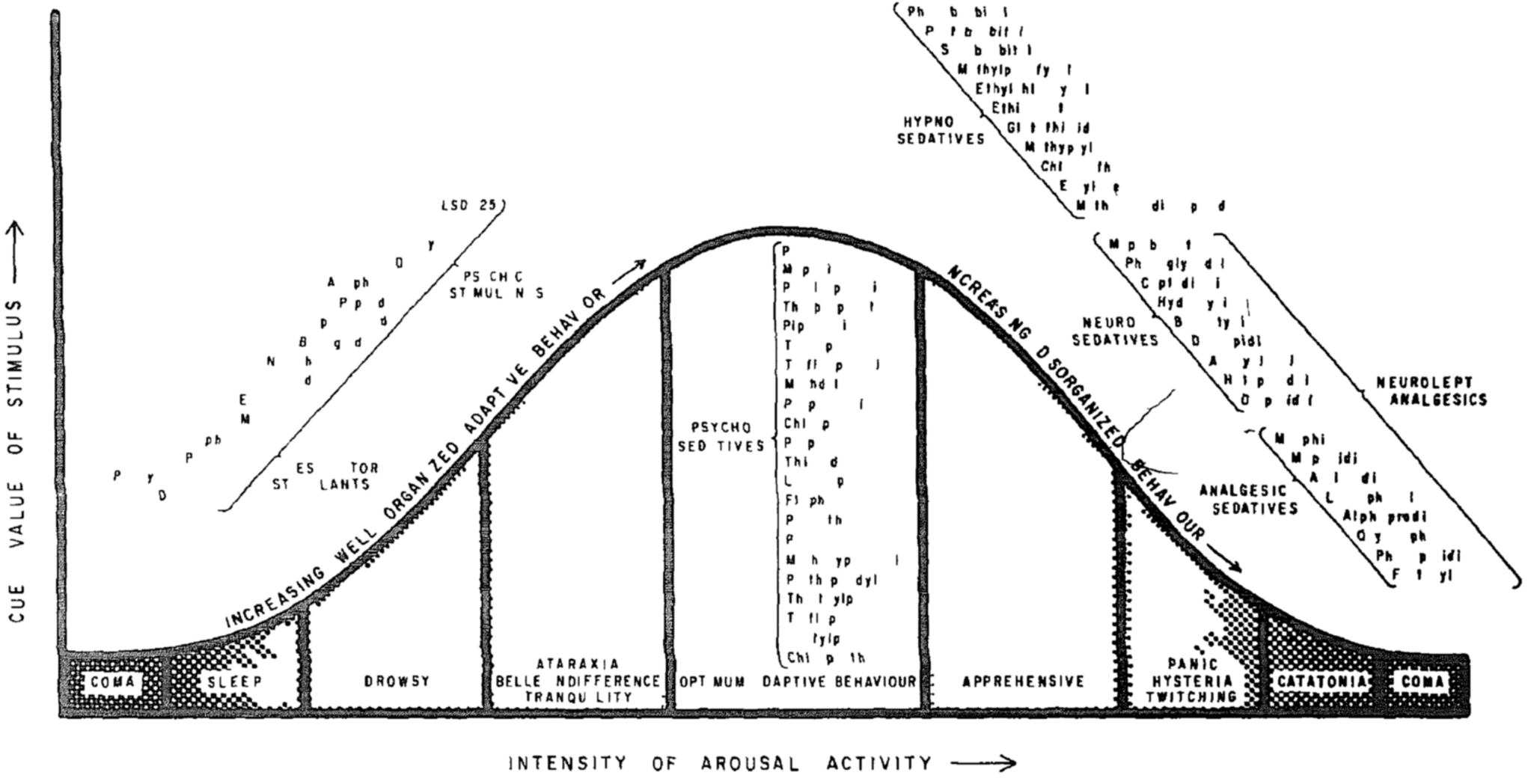


FIGURE 2 Grouping of sedative and stimulant drugs according to their effect on arousal activity and on responsiveness to external stimulation

mild sensory deprivation, that enforces drowsiness or sleep—to a potent neurosedation—which depresses the motor overactivity seen in anxiety and tension states

Biochemically, these drugs have varying degrees of antiepinephrine-antinorepinephrine, antiacetylcholine, antiserotonin, and antihistaminic activities, which change the balance among these neurohormones, and may cause a block or "derailment" of the transmission of various impulses Conversely, they may facilitate and produce excessive nervous (motor and sensory) stimulation [12-16] Perhaps this may explain why some of these drugs (e g promethazine and perphenazine) occasionally produce marked restlessness and a "twitchy" feeling the subject becoming as tranquil "as a cat on a hot tin roof", while others, such as levomepromazine (methotrimeprazine), can produce such intense sensory deprivation that its properties cannot be distinguished from those of a potent analgesic drug such as morphine [17 18]

On the right side of Figure 2 is a list of sedative drugs, which are divided into three groups hypnosedatives, neurosedatives, and analgesic sedatives

Many of the hypno- and neuro-sedatives are difficult to prepare for parenteral use Their action is relatively slow in onset, but when given in adequate dosage they are very useful agents for providing several hours of sleep Aside from hangover after wakening, they have no appreciable side-effects Chlordiazepoxide (Methaminodiazepoxide, Librium) is the newest among these and is now available for parenteral use When given by this route, it appears to be very effective for providing light, relaxed sleep I have used it as the sole hypnotic-neursosedative for elderly patients receiving spinal anaesthesia The sedation it provides is unsurpassed, because a single dose causes excellent sedation, and it is entirely free of undesirable effects It is equally effective for sedation before general anaesthesia [19]

Most of the neurosedatives are not of particular value to the anaesthetist for use in premedication because their action is too weak after a single administration When a large dose is given parenterally, severe toxic effects occur too frequently and annul any value they might possess Some of these stimulate the basal ganglia, causing the release of acetylcholine which, in turn, produces a restless subject, or one with severe neuromuscular disturbances (e g grinding teeth, torticollis) This reaction can be relieved by administration of an anticholinergic drug such as atropine or benztropine Such a reaction is rarely seen with the phenothiazine derivatives after a single administration, but it is a common reaction to haloperidol—which frequently causes a *delayed reaction* of this kind [20] Among these neurosedatives, hydroxyzine (a diphenylmethane), meprobamate (a propanediol), and droperidol (a butyrophenone) are the most active and are currently viewed as very useful sedatives for preoperative sedation

Greater advantage may be taken of some of the hypnotic and neuro sedatives for use in clinical anaesthesia by combining one of them with a potent, nonaddicting analgesic drug By careful selection among the drugs in Table I, the undesirable effects of a pair may be mutually blocked, and their useful effects enhanced Such drug combinations have been used to provide "alert analgesia" or "neuroleptanalgesia," and are discussed in the following section

"Alert Analgesia," Neuroleptanalgesia, Nothria

Two or more anaesthetic agents have been combined ever since Clover used nitrous oxide to facilitate induction of anaesthesia with diethyl ether, and diethyl ether to reduce the amount of chloroform required for maintenance of anaesthesia [21] After the turn of the century, no serious attempts were made to extend this idea because of the paucity of available drugs In 1926, Lundy suggested the use of a balanced anaesthetic technique, which consisted of sedative drugs for premedication, light general anaesthesia, and the additional use of regional anaesthesia to reduce the amount of toxic general anaesthetic drugs required This technique satisfied Crile's physiological reasoning, that regional anaesthesia should be used to suppress the noxious stimuli from the operative site, allowing psychic depression (unconsciousness) to be achieved with much less general anaesthesia [22] Today, this concept is applied widely

After Griffith introduced curare for muscular relaxation, in 1942, attempts were renewed to combine agents physically In 1947 Baird combined thiopental and *d*-tubocurarine in a fixed mixture (100 3) for intravenous use,[23] reinforced by nitrous oxide Many of the physicians he trained still favour this technique About the same time, others combined the inhalation of nitrous oxide with parenteral curare[4 24] or meperidine [2] After the introduction of the phenothiazine derivatives as adjuncts to anaesthesia by Laborit and Huguenard, a fixed combination of chlorpromazine, promethazine, and meperidine had a short period of popularity, and became known as the 'lytic cocktail" Since their enthusiastic reports appeared, the ever-growing number of potent psychosedatives encouraged attempts at similar combinations of phenothiazines with other analgesic drugs [25]

During the past six years, a lull in these attempts became obvious because of the wide-spread adoption of halothane Although this agent has many desirable properties, there were a few who feared its potential dangers, particularly with respect to the occurrence of cardiorespiratory depression, and they began to favour its azeotropic mixture with diethyl ether, which Hudon and his associates first employed New fears have now arisen that halothane may have hepatotoxic properties, that were perhaps not recognized earlier Even though this possibility is obviously remote, and perhaps reflects the use of halothane with abandon or without composite skill and judgment, substitute anaesthetics are eagerly being sought again

In the meantime, the concept of general anaesthesia has been reviewed in the light of the growing versatility provided by so many new parenteral drugs Little and Stephen expressed the need for employing a combination of drugs in a way that they called *modern balanced anaesthesia*,[26] in order to improve patient care, and Woodbridge looked into the terminology used in anaesthesia and felt that our efforts to provide a balanced depression of the sensory, motor, reflex, and mental modalities by appropriate drugs should be called *nothria* [27]

In 1959, Janssen introduced two new groups of drugs One, the butyrophenones, has neuro- and psycho-sedative properties similar to those of the phenothiazines The other (meperidine-like) has analgesic properties of great potency, possibly with little propensity to addiction In Europe, the combination of these drugs has been well demonstrated by DeCastro and Mundeleer, and they have called

this *alert analgesia* or *neuroleptanalgesia* because the analgesia is intense whereas the sedation causes little or no hypnosis [28-31]

Nilsson described the term neuroleptanalgesia as the anaesthetic technique in which the patient is premedicated with a drug which causes a state of apathy and akinesia, to which is added a drug which is a potent analgesic He has outlined the value of combining a potent analgesic with a neurosedative, but feels that there is no advantage to having a patient awake during the apnoea produced by such mixtures, and favours the use of nitrous oxide to render the patient unconscious [32 33,34] He has had only limited success with this method, perhaps mainly because the individual drugs were not yet sufficiently studied and human bio-assay is a slow and tedious task [35] At first, the analgesics dextromoramide and phenoperidine were combined with the neurosedative haloperidol [36,37 38] Human bio-assay of haloperidol has shown that it causes a relatively high incidence of cholinergic reactions, so the idea of using it in anaesthesia may be abandoned,[20] even though some anaesthetists have lauded its use [39]

Currently, a closely related pair, having the generic names droperidol (sedative) and fentanyl (analgesic) are being tried These have been combined in a 50 1 mixture now known as Innovan [40 41] Given together with nitrous oxide, this combination provides excellent analgesia and hypnosis for operations not requiring muscular relaxation Circulatory stability (blood pressure, heart rhythm, and rate) attending this anaesthetic is a prominent characteristic Severe respiratory depression occurs, but its duration is relatively short An interesting difficulty caused by this mixture is rigidity of skeletal muscles, especially in the thoracic cage, which is probably due to the cholinergic action of the analgesic This effect can be relieved by the administration of a small dose of muscle relaxant It will be interesting to see if more disturbing cholinergic reactions will occur with this mixture several hours after terminating a clinical anaesthetic

It is worth comparing this mixture with combinations of more widely known intravenous agents having hypnotic, analgesic, and anti-emetic properties, for we may then find numerous mixtures that might surpass in efficacy the currently available agents [41] However, there is one point that should be kept in mind if intravenous mixtures such as the one described above come into common use once injected, they are irretrievable and we cannot back away as easily from an untoward response as is possible with inhalation agents, and it is more difficult to know what antidote to use in a given case, since we are always dealing with at least two drugs with rather different properties

There is one other aspect of this form of anaesthesia which is worthy of consideration it is clear that the patient may be conscious during this kind of anaesthesia, as noted by Nilsson [34] When general anaesthesia is to be used, most patients expect not only complete freedom from pain, but they usually desire also a complete removal of conscious awareness, *especially when they cannot breathe without help* [42] It is therefore important to regard this form of anaesthesia as one requiring enough nitrous oxide to keep the patient "asleep," and the anaesthetist must be prepared to augment respiration at least to the end of the surgical procedure at which time he may have to administer an antinarcotic drug, and perhaps also an anticholinergic drug Unfortunately, it is not feasible to administer the antinarcotic drugs *during* anaesthesia, for with analgesics such as phenoperidine

and fentanyl all of the pharmacological effects are reversed by drugs such as nalorphine and levalorphan

ANTIDOTES

Mention of the word analeptics among anaesthetists frequently conjures up the vision of a cyanotic, frothing, convulsing patient, vainly gasping for breath Thought on this subject has become so rigid that it is more sensible to apply the term "antidote" to all supportive drugs and gases [4,43,44 45] We may administer oxygen and augment pulmonary ventilation to prevent or reverse hypoxia, prostigmine or edrophonium to terminate skeletal muscle paralysis due to curariform drugs, respiratory and cortical stimulants to counteract severe hypnotic depression, antinarcotics to restore wakefulness and augment pulmonary ventilation which has been depressed by narcotic analgesics and vasopressors to restore adequate peripheral vasomotor activity In most instances, we also administer atropine or other potent anticholinergic drugs to reduce the production of oropharyngeal secretions, relax the tracheobronchial tree, prevent vomiting, and block the cholinergic effect of several of the sedatives and a few of the antidotes (prostigmine, edrophonium) (Table III)

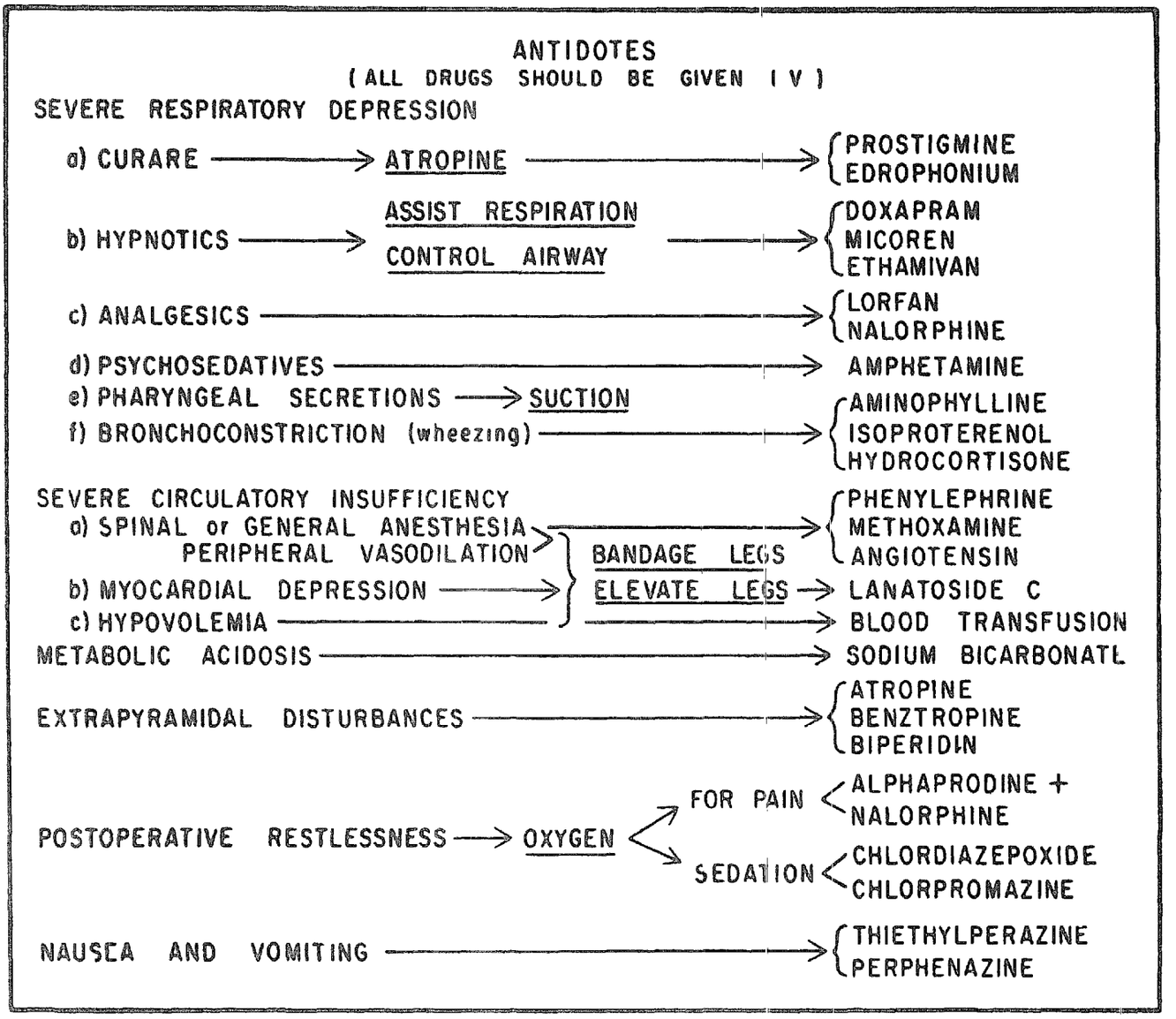
At the termination of every general anaesthetic, the removal of intense sensory stimulation and the persistence of the potent hypnotic and analgesic effect of the anaesthetic *promote* the occurrence of severe respiratory depression This condition is aggravated by the hypoxia which may be due to the outward diffusion of the anaesthetic gases Our efforts at this time should therefore be directed to increasing the depth and reducing the effort of breathing, reducing peripheral vasodilation and preventing cardiovascular depression, shortening the period of unconsciousness and depressed reflex activity, augmenting the elimination of inhaled anaesthetics, reversing the action of injected depressants and restoring metabolic homeostasis [46 47 48]

It is unfortunate that many anaesthetists are reluctant to use antidotes because they feel that such action is tantamount to admission of failure in the management of the anaesthetic or that adequate skill was not exercised Even if this were the case, on occasion, why let the patient suffer and prolong their own agony? Although it is irritating to listen to wailing adults and crying children, we should be pleased when our patients are virtually wide awake soon after the end of an anaesthetic and are lucid enough to complain of their morbid state, for then they will usually breathe better, and circulatory homeostasis will probably return faster Suitable measures can then be taken to make them more comfortable without causing excessive depression of vital functions

Recently, I heard the following comment by an anaesthetist "Some people set great store in the patient talking in the operating theatre as soon as the anaesthetic ends, but I have yet to hear of a case in which the patient has made any valuable contribution to knowledge or conversation at that time" This clinician undoubtedly was fortunate in having a well-staffed recovery room or intensive care unit where his "poisoned" victims could be watched vigilantly until they recovered and where he didn't have to listen to any profound statements Other clinicians have caused difficulty by their actions, for, at the first sign of active life following an operation, they promptly order a substantial dose of a

TABLE III

SUMMARY OF SOME ANTIDOTES THAT ARE GENERALLY USED IN ANAESTHESIA, AND THEIR SPECIFIC INDICATIONS



narcotic analgesic and return the patient to oblivion, with attendant severe respiratory depression Pain-relieving drugs administered in the immediate postoperative period certainly cause more pulmonary complications than does infection, because they not only augment the respiratory depression due to the persistence of anaesthesia, but they often provoke vomiting (and aspiration) and cardiovascular depression—which help to account, in part, for postoperative mortality, especially in those patients who already have chronic disease of the heart and lungs [46]

Assurance of an uneventful anaesthetic recovery is greatly augmented if early wakefulness occurs after a general anaesthetic In the conscious healthy patient, about one-third of the normal resting breathing is driven chemically, the remainder being due to the wakeful stimulus (Fig 3) [49 50 51] Fink has demonstrated this by administering two successive equal doses of thiopental The first caused severe respiratory depression and a period of apnoea After recovery of respiration, but *before* recovery of wakefulness, the second injection caused much less respiratory depression and did not cause apnoea

To restore wakefulness at the end of an anaesthetic without use of stimulant

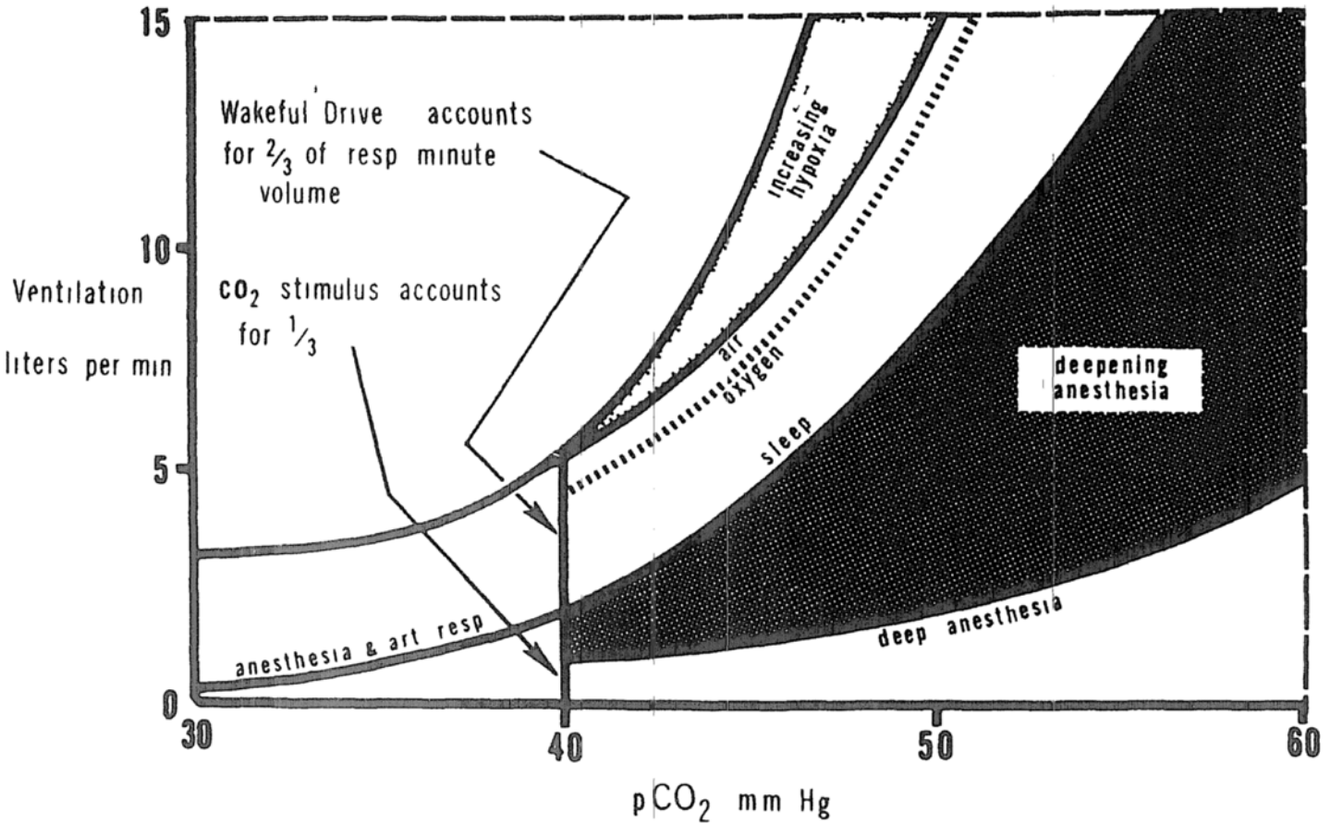


FIGURE 3 The wakefulness-associated stimulus to respiration explains in part why the onset of rhythmic breathing often coincides with the first signs of wakefulness at the end of controlled hyperventilation anaesthesia, as well as at the beginning of life Observe that depression of this stimulus with the onset of sleep accounts for the sharp decrease in sensitivity to carbon dioxide at this time Oxygen breathing causes a slight decrease in sensitivity, whereas increasing hypoxia causes a moderate increase in the sensitivity to carbon dioxide

drugs requires considerable skill and judgment, which can be acquired only after long practice Several of the drugs listed on the left side of Figure 2 can be used in a dilute infusion with 5 per cent dextrose in water to hasten recovery They are also useful in that their administration may be employed to indicate whether intercostal or diaphragmatic paralysis is present because of a persistent action of a muscular relaxant, by watching for spasmodic movements of the diaphragm, intercostal muscles, and larynx accompanying the rapid development of signs of wakefulness If this occurs, an appropriate dose of edrophonium or prostigmine can be given a few minutes after administration of atropine, provided that succinylcholine has *not* been used If succinylcholine has been used, breathing should be assisted until spontaneous efforts become effective and adequate

It is wise in caring for patients with severe emphysema or other types of severe pulmonary impairment to give an antinarcotic drug such as nalorphine or levalorphan whenever narcotic analgesics are required postoperatively for the relief of pain Alternatively, nikethamide (1000 mg), ethamivan (500 mg), micoren (500 mg), or doxapram (200 mg) may be given by dilute infusion until the patient is clinically wide awake (Fig 4) In cases of prolonged anaesthesia, considerable blood loss, interference with the main vascular tree, and severe surgical trauma, mannitol promotes restoration of urinary excretion, and sodium bicarbonate reverses the occurrence of postoperative metabolic acidosis Sodium bicarbonate also appears to be effective in promoting early recovery of wakefulness [52]

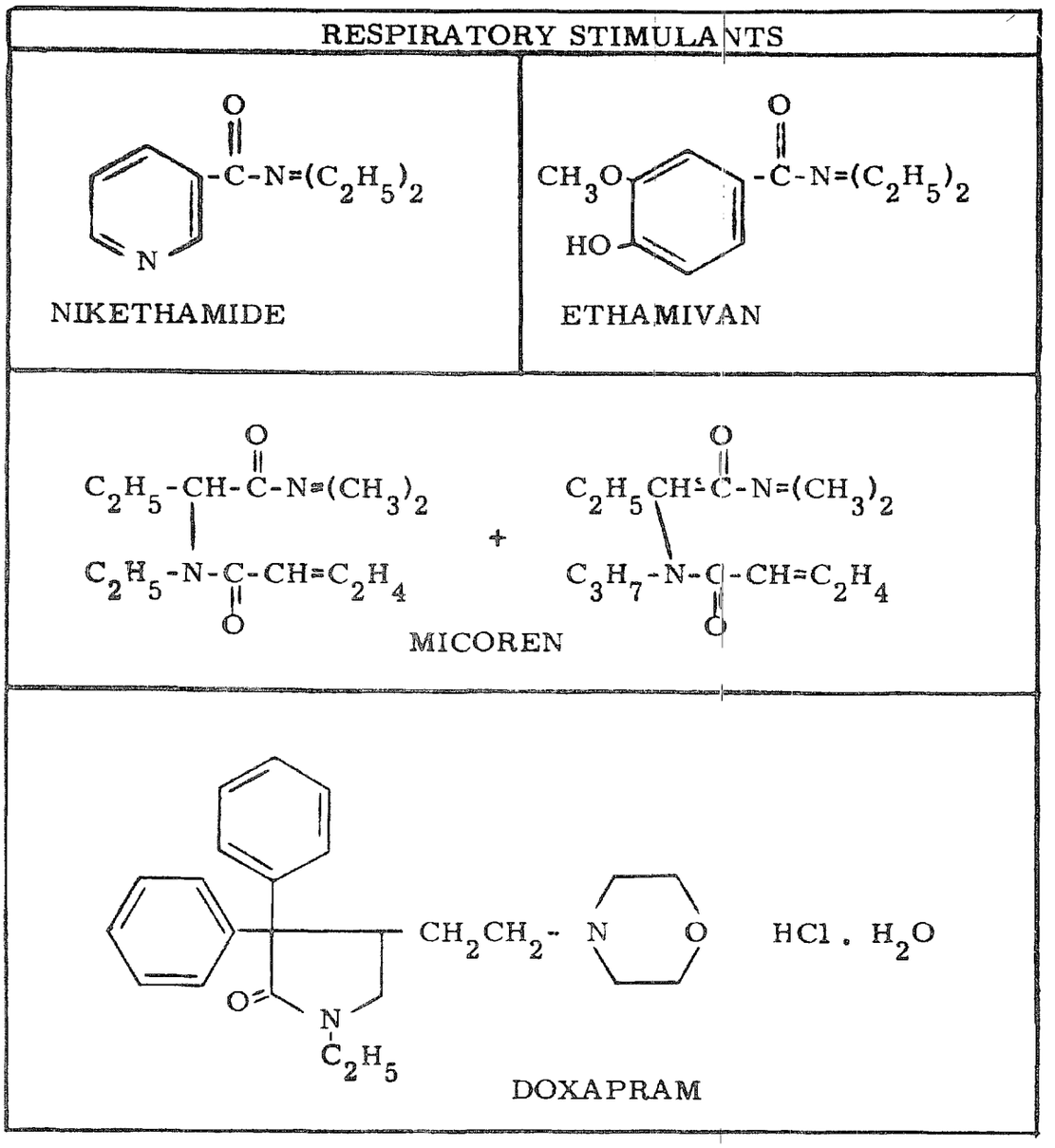


FIGURE 4 Structural formula of some respiratory stimulants These are most effective when used in a dilute intravenous infusion rather than by single injection

INTERACTION OF DRUGS USED IN ANAESTHESIA

Of special interest to the anaesthetist is the effect of drugs which provoke alterations in the circulating blood level of endogenous substances such as adrenaline, amine oxidase and its inhibitors, anticholinesterases, acetycholine, antihistaminics, histamine and 5-hydroxytryptamine and their degradation products, for in many instances these substances influence the primary physiological responses to anaesthesia, and can determine the degree of desirable and undesirable reactions we may expect from a particular anaesthetic or ancillary drug A few of these are depicted in Figures 5A and 5B

Methods have now been developed which make it much easier to study the effect of anaesthesia on the concentration of these endogenous substances in the circulating blood [53 54 55] Data of this kind help us to explain also some of the troublesome effects of anaesthetics [12-16 56,57]

Detailed knowledge of the interaction of two or more drugs in the human body has become very important because of the general trend to use of combinations of drugs with diverse action, but investigation of this subject presents such

complicated aspects of biochemistry, pharmacodynamics, and psychochemistry that it has been difficult to study it adequately in a clinical setting Nevertheless, for the sake of safety alone, great strides must now be made [35] There is no doubt that, among clinicians, the anaesthetist has the most practical experience with the use of drug mixtures, and he has also the best opportunity to expand available information on this subject

Pharmacologists who have studied the interaction of drugs have been concerned with the confusing terminology used in discussing these interactions [58 59 60] For our purposes and for the sake of simplicity, drug interactions can be discussed most easily if we open our thoughts initially to two general terms synergism and antagonism

Veldstra[60] defines synergism as follows the combination of drugs effects a certain response with a smaller number of molecules than that required for the most active compound separately, or in the range of suboptimal concentrations the effect of a certain number of molecules of the compound is enhanced by the mixture This definition has been applied to the terms *potentiation* and *addition* as well

Schild, Loewe, and others have dealt with the far more complex problem of drug antagonism and antagonists [61-64] From the anaesthetist's point of view the conditions that must be considered here are the route of administration, the therapeutic dose range of drug pairs, the relative time of administration of each of the partner drug doses, synchronization of time of administration with regard to "time of peak effect" or some specified starting point for action of the two partner doses, and duration of the principal action of the partner drugs to some specified end-point of activity

The first step in determining the effect of two drugs is to construct dose response curves for each of the partner drugs with respect to their primary pharmacological effects (e g analgesia) and their prominent undesirable side-effects (e g vomiting, apnoea), as shown in Figures 1A and 1B Then, in dealing with the combination of drugs, the place of the effect in the ordinate is replaced by the partner drug, and lines are drawn connecting those dose pairs which are equally effective with regard to an adequately selected end-point This is similar to the cartographer's method adopted by Loewe [62]

Gaddum has shown a way of depicting such experimental data[65] as follows When two drugs that have a similar effect (e g hypnotic sedation) are combined, the ordinate represents the doses which produce progressive effectiveness with respect to a predetermined end-point (such as unconsciousness) Similarly, the abscissa represents the doses of the partner drug which produce progressive effectiveness with respect to the *same* end-point (see Fig 6A) If the end-point effect is produced by combinations of the two drugs represented by points inside the rectangle *OACB* the drugs are helping one another This is called synergism If the end-point effect is just produced by combinations represented by points on the straight line *AB*, the effects are said to be additive If the effect is produced by points in the triangle *OAB*, the effects may be said to be potentiated—i e, the drugs produce more effect than would be expected by simple addition

If the presence of drug B necessitates the presence of a greater quantity of

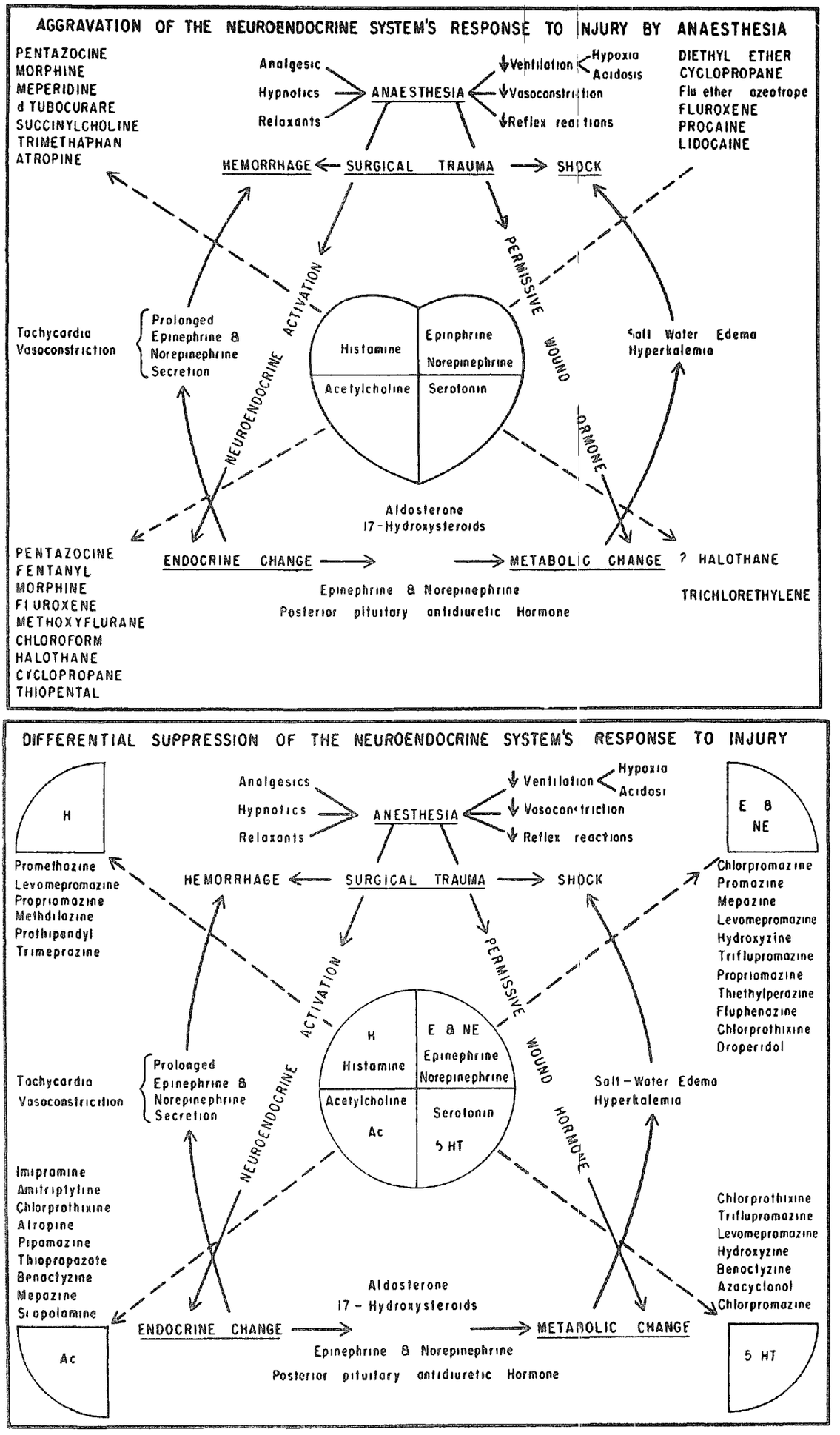


FIGURE 5 A Aggravation of the neuroendocrine system's response to injury by anaesthesia B Differential suppression of the neuroendocrine response to injury

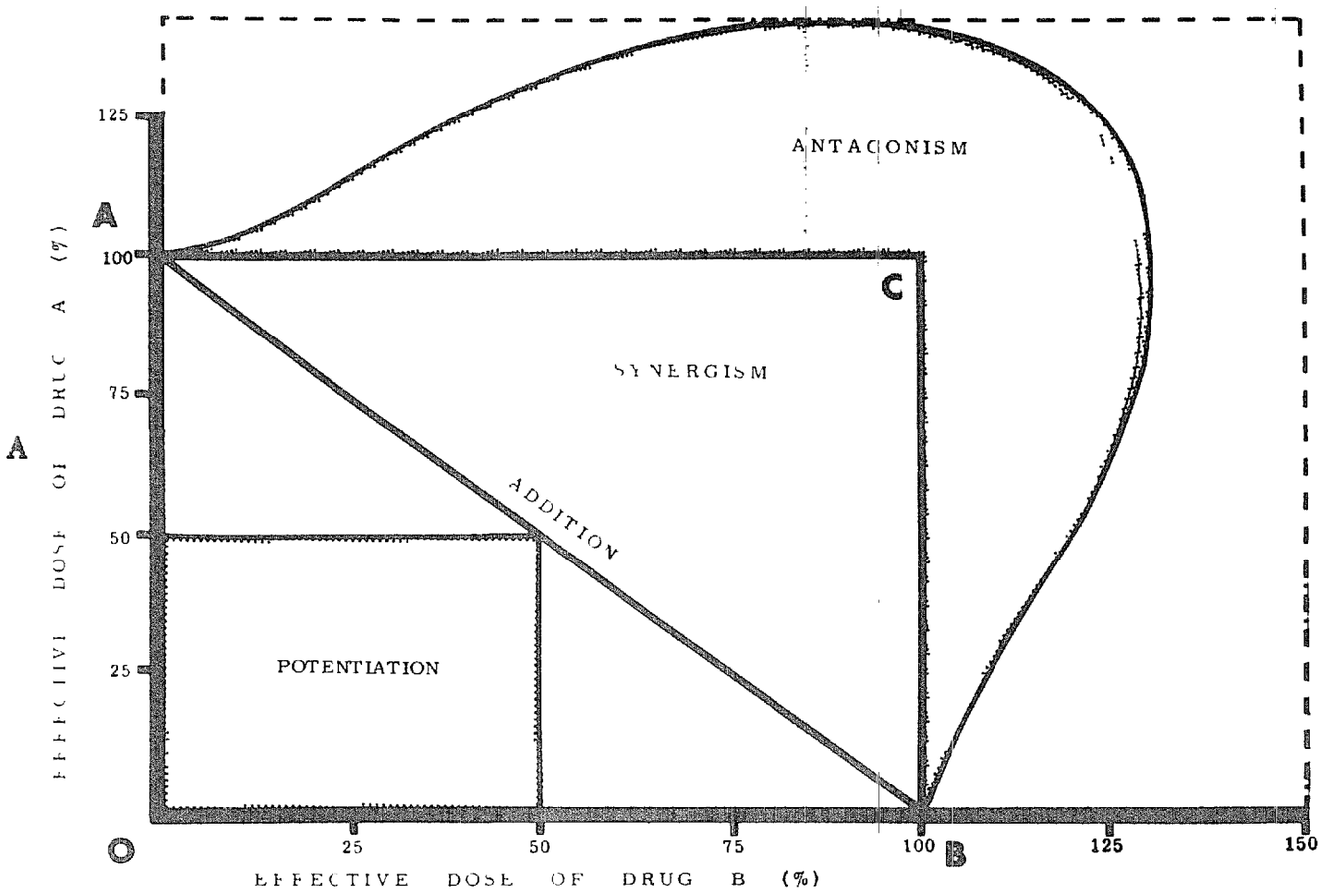
drug A than would be required to reach the same end-point by itself, drug B is antagonizing the effect of drug A, and the effect would be represented by points *above* line *AC* Similarly, points *to the right* of line *CB* indicate that drug A is an antagonist with respect to the effect of drug B

Gaddum recommends that the simplest way of defining the effect of an interaction is to administer half the "effective dose" of each of two partner drugs If the combination causes the end-point effect, the actions of the two drugs are additive, if the effect is much more, potentiation is occurring, if the effect is much less, some form of antagonism is occurring When the effect of antagonistic drugs is plotted by combining the LD_{50} of one partner drug with various doses (LD_5, LD_{50}, LD_{95}) of the antagonistic partner, the line representing the dose pairs with a combined LD_{50} effect is the "isobol" for that pair For combinations of doses which fall above the isobol the antagonism is insufficient to reduce mortality appreciably, whereas for points below the isobol, the antagonism is more effective and the mortality rate is reduced The efficacy of various mixtures using sublethal doses of the partners can be determined for several clearly defined end-points

Although this approach to the study of drug combinations is time-consuming and perhaps cumbersome, it yields valuable information, as is evident from the excellent studies by Eerola,[66] who used this technique to demonstrate clearly that the effect of the interaction of ethanol on toxicity of tranquillizers is an additive synergism, slightly less than the algebraic sum of the individual drug effects, and by Maykut and Kalow, who demonstrated the interesting hypnotic and toxic effects when procaine and pentobarbital are combined[67] (see Fig 6B)

Current information on this subject is too involved for detailed discussion here, but one idea is worth noting [60] The effect of the combined action of two compounds having the same primary site of action will not necessarily result in synergism, but will generally even be unfavourable It appears that the competition for the drug receptor usually *decreases* the frequency of the best interactions And, when the components of a combination of drugs possess different sites of action, and different types of activity, no plausible prediction about the possibility of synergism or antagonism can be made *unless their mode of action is well known* This concept is quite different from the old law of Burgi, which stated In combining drugs with the same end-effect, the resulting activity is additive when the sites of action of the components are identical and superadditive if they are different [68]

Some examples of interactions which are important to the anaesthetist are as follows Acetylcholine action can be enormously enhanced by cholinesterase inhibitors such as physostigmine, possibly by retarding its enzymatic decomposition [69] Cocaine in combination with adrenaline has a synergistic effect on the pressor and mydriatic actions of the latter, possibly by inhibition of adrenaline oxidation by the local anaesthetic ("pharmacological deprivation") [70] Iproniazid (a monoamine oxidase inhibitor) markedly prolongs the action of serotonin possibly because monoamine oxidase inhibitors are potential synergists with respect to serotonin [71] Some ill-defined property of drugs with parasympathomimetic action (choline, neostigmine, physostigmine) enhances the action of analgesics



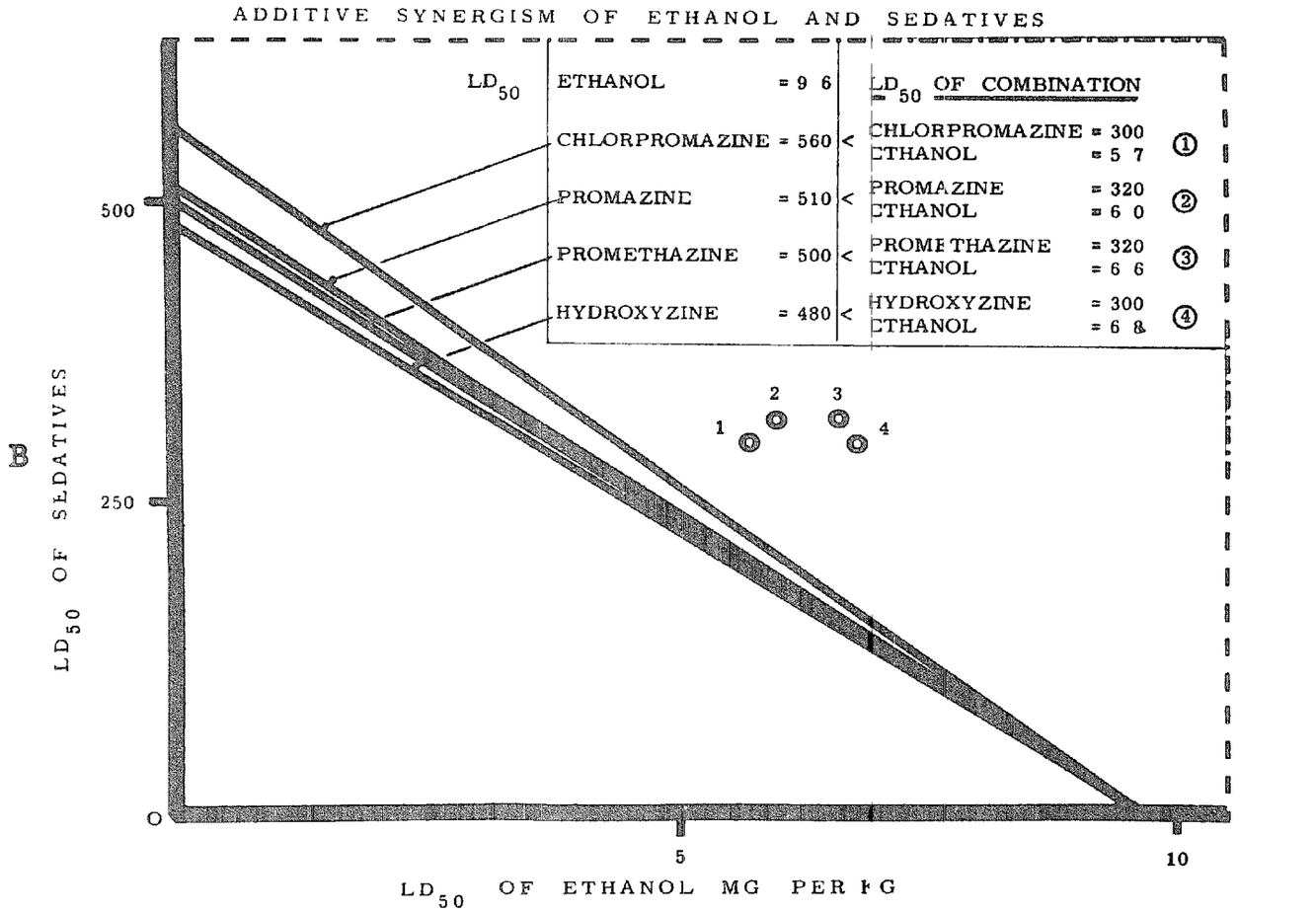


FIGURE 6 A Gaddum's method of demonstrating graphically the interaction of two drugs used in combination B Example from Eerola[66] showing the effect of interaction of ethanol and four sedatives on LD_{50} of mice

such as morphine, possibly by a competitive antagonism with respect to molecules of the analgesic adsorbed to "silent receptors," thus rendering available more molecules of the analgesic for its primary action [72] Alcohol does not have a potentiating effect on the hypnotic depression produced by barbiturates but rather an additive effect, which is dependent upon the method of administration,[66 73] and is due possibly to an increase in the sensitivity of the tissues in the central nervous system [74] Antihistaminic drugs (e g diphenhydramine and promethazine) as well as histamine prolong the sleeping time of some barbiturates,[75 76 77] possibly because of an increased rate of penetration of the barbiturate into the brain under the influence of the antihistamines, and perhaps by inhibiting pyruvate oxidation in brain tissue, as well as by selective interference with glutamate oxidation [78,79] Chlorpromazine, reserpine, and serotonin increase the sensitivity of the central nervous system to barbiturates by a mechanism which is still obscure [80 81]

Nickerson has pointed out that we have agents which form stable bonds with a variety of specific receptors and provide an important tool for the analysis of drug effects on endogenous substances in the body Knowledge of the distinct receptors for adrenaline, histamine, acetylcholine, and serotonin make it possible to study the mechanism of action of our anaesthetic drugs with far greater definition and may help to explain some of the effects described above [63 64 82]

Many dangerous interactions have come to the attention of the anaesthetist vicariously A deleterious reaction to induction of anaesthesia, or failure of respiration at the end of an uneventful anaesthetic, has frequently heralded the first sign of an undesirable interaction of drugs Dundee[83] has reviewed a number of these the hypotensive action of analgesics and anaesthetics becomes difficult to control if the patient has been taking reserpine, or other antihypertensive drugs The development of adrenocortical insufficiency due to prolonged use of cortisone and its analogues sets the stage for cardiovascular collapse if an anaesthetic is given Recently, it was found that several of the broad spectrum antibiotics can cause severe respiratory depression following their peritoneal installation by a blocking action on neuromuscular transmission This effect is particularly prominent following anaesthesia with ether and curare [84 85] Coma may occur in patients receiving amine-oxidase inhibitors if they are premedicated with a narcotic analgesic,[86] and alcohol can potentiate the lethal effect of an overdose of sedative drugs [87] As more therapeutic agents are added to the physician's store of medications, the list of serious interactions with anaesthetics will certainly grow longer

We are all particularly aware that the desirable sedative response to psychosedatives is not consistent[88] and that synergism of their undesirable effects occurs when they are combined with other drugs [89 90] If we resort to a form of anaesthesia which, by its nature, depends on the combination of several drugs with diverse actions, the difficulties that might arise are awkward to cope with, because it is at present too complicated to analyse the mechanism of their combined action, unless a representative variety of combinations is studied first in a carefully devised experiment designed to reveal all the probable short-term and long-term effects that these drugs are capable of causing, either alone or in combination

Commentary

My purpose in this review is to present a look at a large number of new drugs, many of which have been recommended for trial in anaesthesia, and to suggest that we now have the possibility of combining some of these drugs in such a way that more of the desirable features of a safe and pleasant anaesthetic can be developed than was ever possible before, with fewer physiological and metabolic disturbances in our surgical patients

Two precautionary reservations should be considered seriously prior to using these new drugs in anaesthesia First, we must know and understand all the acute effects that the new drugs (or combinations of drugs) are capable of producing. Second, we should not, in our present state of knowledge, complicate an anaesthetic unnecessarily by using a combination of parenteral anaesthetic agents in a poor-risk patient when we can give a simpler, safer, and more satisfactory anaesthetic with an inhalation agent such as cyclopropane, methoxyflurane, halothane, fluroxene, or diethyl ether alone or reinforced with a relatively non toxic concentration of nitrous oxide

The anaesthetist has been depicted by Bickford as a human linkage in a feedback system which is essentially error-actuated [91] Now, we are trying to develop to a stage where we can predict and prevent variations that are deleterious to our patients, as well as to devise combinations that are safe and have greater efficacy than single agents However, our knowledge is still too meagre to adopt the general use of drug combinations From our point of view, the most important aspect of the patient's welfare involves mainly his respiration, his circulation, and his parenchymatous organs If we can find a sedative drug that causes adequate preoperative psychic relaxation, an anaesthetic that provides deep sensory deprivation and light hypnotic depression (or unconsciousness), and then if we can restore wakefulness and adequate pulmonary ventilation promptly without depressing liver function or circulatory dynamics, we shall have gone a long way towards providing safer anaesthesia

Before we enthusiastically embrace the wide variety of new and potent agents, each one of us should first learn what the relatively healthy patient's response might be to such agents, alone, and then in combination with our anaesthetics, especially those whose pharmacological actions require far greater definition in man and whose individual efficacy has yet to be proved [92 93] Those physicians who are oriented towards pharmacodynamics and biochemistry must help us to clarify further the action of anaesthetic drugs on the secretion of the several known active brain substances,[94] their relationship to endocrine effects,[95] and how the body is ultimately affected by these interactions [96-99] Careful clinical observations alone cannot give us the vital answers we seek

New agents are being presented to us so rapidly that we can only improve our patient's anaesthesia by carefully evaluating these before using them on the very ill But, to be sure that what is new is in fact much better requires the active participation of far more clinicians than are currently engaged in such studies

Résumé

Dans ce travail, j'ai tâché de faire la lumière sur un bon nombre de nouveaux médicaments, dont plusieurs ont été mis à l'essai en anesthésie, j'ai exprimé l'idée

que nous pouvons maintenant associer un certain nombre de ces médicaments afin de réaliser une anesthésie plus agréable et plus sûre, tout en diminuant l'atteinte physiologique et métabolique chez nos opérés

Avant d'utiliser ces nouveaux médicaments en anesthésie, il faut faire deux prudentes réserves D'abord, il faut connaître et comprendre tous les effets immédiats que ces nouveaux médicaments (ou leur association) peuvent produire En second lieu, dans l'état actuel de nos connaissances, nous ne devrions pas compromettre inutilement les résultats d'une anesthésie chez un malade qui présente un mauvais risque, en injectant à ce malade un mélange d'agents anesthésiques, il vaut mieux donner une anesthésie plus simple, plus sûre et plus satisfaisante, en utilisant non pas la voie parentérale mais la voie respiratoire et des agents tels que le cyclopropane, le méthoxyflurane, l'halothane, le fluroxène ou l'éther, seuls ou associés au protoxyde d'azote, relativement peu toxique

Bickford décrit l'anesthésiste comme un être intermédiaire qui profite de l'expérience de ses prédécesseurs et cherche à éviter leurs erreurs Maintenant, nous tâchons de prévoir et de prévenir les écarts dommageables à nos malades, et nous cherchons des associations qui, en toute sécurité, sont plus efficaces que des agents utilisés seuls Cependant, nos connaissances sont encore trop vagues pour que nous généralisions l'usage d'associations de médicaments A notre point de vue, pour assurer au malade le maximum de sécurité, il faut tenir compte surtout de sa respiration, de sa circulation et de ses organes parenchymateux Si nous pouvons trouver un sédatif qui produit une bonne détente préopératoire, un anesthésique qui abolit la sensibilité sans provoquer une hypnose trop profonde et si, par la suite, le réveil est précoce et la fonction respiratoire promptement rétablie sans atteinte hépatique ou circulatoire, nous aurons fait un grand pas vers une plus grande sécurité en anesthésie

Avant d'utiliser couramment de nouveaux agents puissants, nous devons connaître l'action de chacun d'eux sur un sujet sain, puis leur action lorsqu'ils sont associés à nos anesthésiques, cette précaution s'impose surtout lorsqu'il s'agit d'agents dont l'action pharmacologique est encore imprécise, et dont l'efficacité reste à prouver Les médecins spécialisés en pharmacodynamie et en biochimie doivent nous aider à préciser l'action des anesthésiques sur la sécrétion des substances cérébrales actives que nous connaissons, leurs effets sur les glandes endocrines, et les résultats de ces actions combinées sur l'organisme humain Les observations cliniques minutieuses ne peuvent à elles seules répondre à toutes nos questions On nous présente si souvent de nouveaux agents que la seule façon d'améliorer notre anesthésie est de connaître à fond ces médicaments avant de les administrer à de grands malades Mais, pour nous assurer que ce qui est nouveau est meilleur, il faudrait que beaucoup de cliniciens s'intéressent à ces études

REFERENCES

1 Dobkin, A B Efficacy of Ataractics in Clinical Anaesthesia—A Review Canad Anaesth Soc J *5* 176 (1958)
2 Brotman, M & Cullen, S C Supplementation with Demerol during Nitrous Oxide Anesthesia Anesthesiology *10* 696 (1949)
3 Eckenhoff, J E & Oech, S R The Effects of Narcotics and Antagonists upon Respiration and Circulation in Man A Review Clin Pharmacol & Therap *1* 483 (1960)
4 Clement, F W Nitrous Oxide-Oxygen Anesthesia, pp 164–171 Philadelphia Lea & Febiger (1951)

5 Dobkin, A B, Keil, A M, & Albano, P C Effect of Micoren, Ethamivan and Nikethamide on Thiopental Recovery Anesth & Analg *41* 58 (1962)
6 Beecher, H K Measurement of Subjective Responses, pp 260 et seq New York Oxford University Press (1959)
7 Adriani, J Premedication An Old Idea and New Drugs. J A M A *171* 108 (1959)
8 Bourne, W Mysterious Waters to Guard, pp 97 et seq Springfield C C Thomas (1955)
9 Nodine, J H & Moyer, J H Psychosomatic Medicine The First Hahnemann Symposium, pp 411–420 Philadelphia Lea & Febiger (1962)
10 Hebb, D O Drives and the C N S (Conceptual Nervous System) Psychol Rev *62* 243 (1955)
11 Arduini, A & Arduini, M G Effect of Drugs and Metabolic Alterations on Brain Stem Arousal Mechanism J Pharmacol & Exper Therap *110* 76 (1954)
12 Vogt, M Concentration of Sympathin in Different Parts of the Central Nervous System under Normal Conditions and after Administration of Drugs J Physiol *123* 451 (1954)
13 Brodie, B B & Shore, P A A Concept for a Role of Serotonin and Norepinephrine as Chemical Mediator in the Brain Ann N Y Acad Sci *66* 631 (1957)
14 Richter, D & Crossland, J Variation in Acetylcholine Content of the Brain with Physiological State Am J Physiol *159* 247 (1949)
15 Miller, R A & Morris, M E Sympathoadrenal Responses during General Anaesthesia in Dog and Man Canad Anaesth Soc J *8* 356 (1961)
16 Murphy, P Histamine in Anaesthesia A Short Survey Brit J Anaesth *34* 397 (1962)
17 Dobkin, A B & Purkin, N Double Blind Study of Phenothiazines Used in Pre-anaesthetic Medication A Clinical Evaluation of Promethazine (Phenergan), Promazine (Sparine) Proclorperazine (Stemetil), and Levomepromazine (Nozinan) Canad Anaesth Soc J *7* 158 (1960)
18 Paradis, B Analgesic and Anaesthetic Properties of Levomepromazine (Nozinan) Canad Anaesth Soc J *9* 153 (1962)
19 Tornetta, F J Clinical Evaluation of Injectable Librium in Preanesthetic Medication Anesth & Analg *42* 463 (1963)
20 Dobkin, A B & Criswick, V G Circulatory Response to Tilt with Some Anti-emetic and Sedative Drugs Canad Anaesth Soc J *8* 387 (1961)
21 Duncum, B M Development of Inhalation Anesthesia with Special Reference to Years 1846–1900 (Series II) New York Oxford University Press (1947)
22 Lundy, J S Clinical Anesthesia Philadelphia Saunders (1944)
23 Baird, J W Pentothal-Curare Mixture Anesthesiology *8* 75 (1947)
24 Geddes, I C & Gray, T C Hyperventilation for Maintenance of Anaesthesia Lancet ii 4 (1959)
25 Laborit, H & Huguenard, P Pratique de l'Hibernothérapie en Chirurgie et en Médecine Paris Masson (1954)
26 Little, D M & Stephen, C R Modern Balanced Anesthesia Anesthesiology *15* 246 (1954)
27 Woodbridge, P D Changing Concepts Concerning Depth of Anesthesia Anesthesiology *18* 536 (1957)
28 Janssen, P A J Verglechende pharmakologische Daten uber sechs neue basische 4'-Fluorobutyrophenone-Derivative Arzneim Forsch *11* 819 (1961)
29 Janssen, P A J A Review of the Chemical Features Associated with Strong Morphine-like Activity Brit J Anaesth *34* 260 (1962)
30 DeCastro, J & Mundeleer, P Anesthésie sans Barbituriques La Neuroleptanalgésie Anesth & Analg *16* 1022 (1959)
31 ——— Neuroleptanalgesia Selection of Drugs, Significance of Analgesia and Neurolepsia. Anaesthesist *11* 10 (1962)
32 Nilsson, E & Janssen, P Neurolept-analgesia, an Alternative to General Anesthesia. Acta Anaesth, Scand *5* 73 (1961)
33 Nilsson, E Experiences with Neuroleptanalgesia Anaesthesist *11* 17 (1962)
34 Nilsson, E Editorial Origin and Rationale of Neurolept-Analgesia Anesthesiology, *24* 267 (1963)
35 Leading Article Interaction between Drugs Lancet ii 818 (1962)
36 Alder, A Erfahrungen mit Neuroleptanalgesi Anaesthesist *10* 322 (1961)
37 Brown, A S Die Neuroleptanalgesie mit Haloperidol und Phenoperidin als neues Narkosverfahren fur neurochirurgische Eingriffe Anaesthesist *11* 22 (1962)
38 Brown, A S, Horton, J M, & MacRae, W R Anaesthesia for Neurosurgery Use of

Haloperidol and Phenoperidine with Light General Anaesthesia Anaesthesia *18* 143 (1963)
39 SAARNE, A Experiences with Haloperidol (Haldol) as a Premedicant Acta Anaesth Scand *7* 21 (1963)
40 HOLDERNESS, M C, CHASE, P E, & DRIPPS, R D A Narcotic Analgesic and Butyrophenone with Nitrous Oxide for General Anesthesia Anesthesiology *24* 336 (1963)
41 DOBKIN, A B, LEE, P K Y, BYLES, P H, & ISRAEL, J S Neuroleptanalgesia A Comparison of the Cardiovascular, Respiratory and Metabolic Effects of Innovan (Droperidol+Fentanyl 50 1) and Thiopentone+Methotrimeprazine (40 1) Brit J Anaesth *35* 694 (1963)
42 Annotation Awareness during Surgery Lancet ii 1394 (1961)
43 HAHN, F Analeptics Pharmacol Rev *12* 447 (1960)
44 CLEMMESEN, C & NILSSON, E Therapeutic Trends in the Treatment of Barbiturate Poisoning The Scandinavian Method Clin Pharmacol & Therap *2* 220 (1961)
45 SELLICK, B A The Use of Antidotes in Anaesthesia Postgrad Med J *31* 468 (1955)
46 MENEELY, G R & FERGUSON, J L Pulmonary Evaluation and Risk in Patient Preparation for Anesthesia and Surgery J A M A *175* 1074 (1961)
47 MILLER, W F, ARCHER, R K, TAYLOR, H F, & OSSENFORT, W F Severe Respiratory Depression Role of a Stimulant, Ethamivan, in the Treatment J A M A *180* 905 (1962)
48 LEDINGHAM, I M & NORMAN, J N Preliminary Communication Acid-Base Studies in Experimental Circulatory Arrest Lancet ii 967 (1962)
49 FINK, R B Influence of Cerebral Activity of Wakefulness on Regulation of Breathing J Appl Physiol *16* 15 (1961)
50 PLUM, F, BROWN, H W, & SNOEP, E Neurological Significance of Posthyperventilation Apnea J A M A *181* 1050 (1962)
51 FINK, R B, HANKS, E C, NGAI, S H, & PAPER, E M Central Regulation of Respiration during Anesthesia and Wakefulness N Y Acad Sci *109* 892 (1963)
52 DOBKIN, A B, ISRAEL, J S, & BYLES, P H Duration of Anaesthesia with Thiopental When Combined with Each of Mannitol, Urea, Sodium Bicarbonate, or Tromethamine ("THAM," "Tris") Canad Anaesth Soc J *11* 159 (1964)
53 VALK, A de T & PRICE, H L Chemical Estimation of Epinephrine and Norepinephrine in Human and Canine Plasma Critique of Ethylenediamine Condensation Method J Clin Investigation *35* 837 (1956)
54 RICHARDSON, J A RICHARDSON, H K, & BRODIE, O J Fluorimetric Determination of Epinephrine and Norepinephrine in Plasma J Lab & Clin Med *47* 832 (1956)
55 WEISSBACH, H, WAALKES T P, & UDENFRIEND, S A Simplified Method for Measuring Serotonin in Tissues Simultaneous Assay of both Serotonin and Histamine J Biol Chem *230* 865 (1958)
56 HAMELBERG, W, SPROUSE, J H, MAHAFFEY, J E & RICHARDSON, J A Catechol Amine Levels during Light and Deep Anesthesia Anesthesiology *21* 297 (1960)
57 ASTON, R, DAN, K, & GREIFENSTEIN, F E Effect of Anesthesia upon Venous 5-Hydroxytryptamine Levels Anesth & Analg, *42* 614 (1963)
58 RENTZ, E Zur Systematik und Nomenklatur der Kombinationswirkungen Arch Int Pharmacodyn *43* 337 (1932)
59 LOEWE, S The Problem of Synergism and Antagonism of Combined Drugs Arzneim Forsch *3* 285 (1953)
60 VELDSTRA, H Synergism and Potentation Pharmacol Rev *8* 339 (1956)
61 SCHILD, H O pA A New Scale for the Measurement of Drug Antagonism Brit J Pharmacol 2 189 (1947)
62 LOEWE, S Antagonisms and Antagonists Pharmacol Rev 9 237 (1957)
63 GADDUM, J H Theories of Drug Antagonism Pharmacol Rev 9 211 (1957)
64 NICKERSON, M Nonequilibrium Drug Antagonism Pharmacol Rev 9 246 (1957)
65 GADDUM, J H Pharmacology, 5th ed, pp 504–5 London Oxford University Press (1959)
66 EEROLA, R The Effect of Ethanol on the Toxicity of Promazine, Chlorpromazine, Promethazine and Hydroxyzine Acta Anaesth Scand 7 87 (1963)
67 MAYKUT, M O & KALOW, W Experiments with Animals on the Combined Action of Procaine and Barbiturates Canad Anaesth Soc J 2 109 (1955)
68 BURGI, E Die Wirkung von Narcotica-Kombinationen Dtsch Med Wschr *36* 20 (1910)
69 KOELLE, G B & GILMAN, A Anticholinesterase Drugs Pharmacol Rev *1* 166 (1949)
70 FLECKENSTEIN, A & STOCKLE, D Zum Mechanismus der Wirkungsverstarkung und

Wirkungsabschwachung Sympathomimetischer Amine durch Cocain Arch Exper Pathol Pharmakol *224* 401 (1955)
71 Sjoerdsma, A, Smith, T E, Stephenson, T D, & Udenfriend, S Metabolism of 5-Hydroxytryptamine (Serotonin) by Monamine Oxidase Proc Soc Exper Biol N Y *89* 36 (1955)
72 Knoll, J & Komlos, E Einfluss des Peptons auf die Wirkung der Analgesika und Parasympathomimetika Acta Physiol Hung *3* 127 (1952)
73 Gruber, C M A Theoretical Consideration of Additive and Potentiated Effects between Drugs with a Practical Example Using Alcohol and Barbiturates Arch Int Pharmacodyn *102* 17 (1955)
74 Sandberg, F A Quantitative Study on the Alcohol Barbiturate Synergism Acta Physiol Scand *22* 311 (1951)
75 Winter, C A The Potentiating Effect of Antihistaminic Drugs upon the Sedative Action of Barbiturates J Pharmacol *94* 7 (1948)
76 Ambrus, J L, Ambrus, C M, Leonard, C A, Moser, C E, & Harrison, J W E Synergism beween Histamine, Antihistaminics and Hypnotic Drugs J Am Pharm Assoc, Sci Ed *41* 606 (1952)
77 Dobkin, A B Potentiation of Thiopental Anaesthesia with Tigan, Panectyl, Benadryl, Gravol, Marzine, Histadyl, Librium, and Haloperidol (R 1625) Canad Anaesth Soc J *8* 265 (1961)
78 Hubbard, T F & Goldbaum, L R Effects of Pyribenzamine on Respiration of Brain Homogenates J Lab Clin Med *35* 284 (1950)
79 Carlisle, E M & Crescitelli, F Selective Inhibition of Brain Respiration by Benadryl Science *112* 272 (1950)
80 Brodie, B B, Shore, P A, Silver, S L, & Pulver, R Potentiating Action of Chlorpromazine and Reserpine Nature *175* 1133 (1955)
81 Shore, P A, Silver, S L, & Brodie, B B Interaction of Serotonin and Lysergic Acid Diethylamide (LSD) in the Central Nervous System Experientia *11* 272 (1955)
82 Furchgott, R F Dibenamine Blockage in Strips of Rabbit Aorta and Its Use in Differentiating Receptors J Pharmacol & Exper Therap *111* 265 (1954)
83 Dundee, J W Iatrogenic Disease and Anaesthesia Brit Med J *1* 1433 (1958)
84 Pittinger, C B & Long, J P Neuromuscular Blocking Action of Neomycin Sulphate J Pharmacol & Exper Therap *122* 61A (1958)
85 Finland, M Kanamycin Lancet II 209 (1958)
86 Taylor, D C Alarming Reaction to Pethidine in Patients on Phenelzine Lancet II 401 (1962)
87 Melville, K I, Joron, G, & Douglas, D Combined Alcohol and Glutethimide or Secobarbital Central Nervous System Potentiation Proc Can Fed Biol Soc, Abstract No 46 (1962)
88 Bodi, T, Siegler, P E, Levy, H A, Slap, J W, & Nodine, J H Human Bioassay in Psychopharmacology The Pharmacologist 2 64 (1960)
89 Calesnick, B, Smith, N H, & Beutner, R Combined Actions of Cardiotoxic Drugs Study on Acute Toxicity of Combined Quinidine, Meperidine, Pentobarbital, Procaine and Procaine Amide J Pharmacol & Exper Therap *102* 138 (1951)
90 Simeone, F A Surgery and Pharmacology Clin Pharmacol & Therap *4* 149 (1963)
91 Bickford, R G The Use of Feedback Systems for the Control of Anesthesia Elect Engng *70* 852 (1951)
92 Melville, K I Editorial Evaluation of New Drugs in Anaesthesia Canad Anaesth Soc J *2* 1 (1955)
93 Gilbert, R B G, Dobkin, A B, & Lamoureux, L Investigation of New Drugs with Special Reference to Largactil as an Example Canad Anaesth Soc J *2* 5 (1955)
94 Quastel, J H & Quastel, D M J The Chemistry of Brain Metabolism in Health and Disease, pp 68–82, 104–111 Springfield C C Thomas (1961)
95 Way, E L & Sutherland, V C Pharmacologically Active Brain Substances and Their Relation to Endocrine Effects Anesthesiology *24* 543 (1963)
96 Van Brunt, E E & Ganong, W F The Effects of Preanesthetic Medication, Anesthesia and Hypothermia on the Endocrine Response to Injury Anesthesiology *24* 500 (1963)
97 Price, H L, Linde, H W, Jones, R E, Black, G W, & Price, M L Sympathoadrenal Responses to General Anesthesia in Man and Their Relation to Hemodynamics Anesthesiology *20* 563 (1959)
98 Vandam, L D & Moore, F D Adrenocortical Mechanisms Related to Anesthesia Anesthesiology *21* 531 (1960)
99 Baez, S & Orkin, L R Effects of Anesthetics on the Response of the Microcirculation to Circulating Humors Anesthesiology *24* 568 (1963)