

Pharmacology of the central GABA-ergic system

2020

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Mother's little helper (Rolling Stones, 1966)



What a drag it is getting old

"Kids are different today,, I hear every mother say

Mother needs something today to calm her down

And though she's not really ill, There's a little yellow pill

She goes running for the shelter of a mother's little helper

And it helps her on her way, gets her through her busy day



"Things are different today,, I hear every mother say

Cooking fresh food for a husband's just a drag

So she buys an instant cake and she burns her frozen steak

And goes running for the shelter of a mother's little helper

And two help her on her way, get her through her busy day

Doctor please, some more of these, Outside the door, she took four more

What a drag it is getting old

"Men just aren't the same today,, I hear every mother say

They just don't appreciate that you get tired

They're so hard to satisfy, **You can tranquilize your mind**

So go running for the shelter of a mother's little helper

And four help you through the night, help to minimize your plight

Doctor please, some more of these, Outside the door, she took four more

What a drag it is getting old

"Life's just much too hard today,, I hear every mother say

The pursuit of happiness just seems a bore

And if you take more of those, you will get an overdose

No more running for the shelter of a mother's little helper

They just helped you on your way, through your busy dying day



Anxiolytic effect

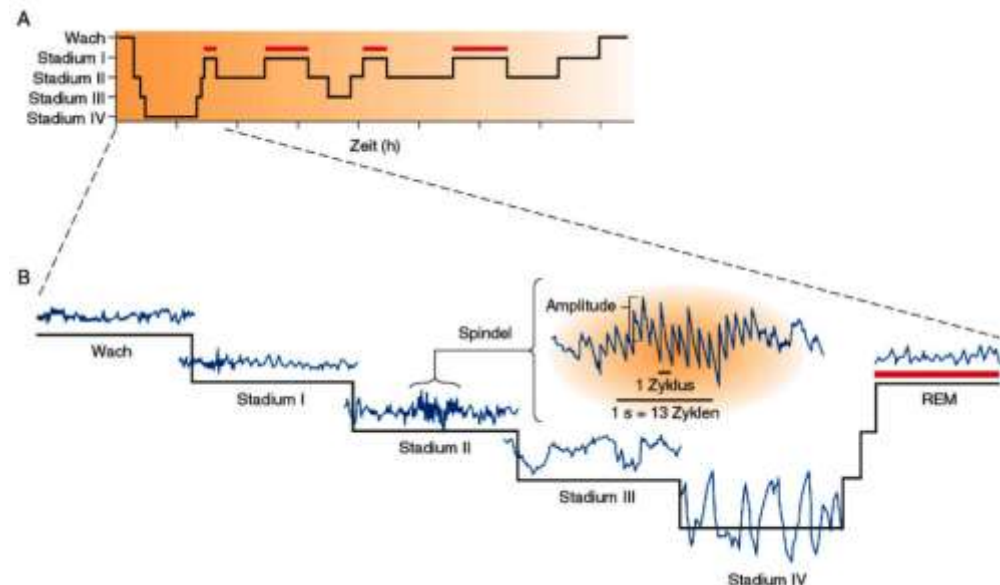
- reduction of anxiety without influencing motor or mental functions

Sedative effect

- suppression of responsiveness to a constant level of stimulation with decreased spontaneous activity and ideation

Hypnotic effect

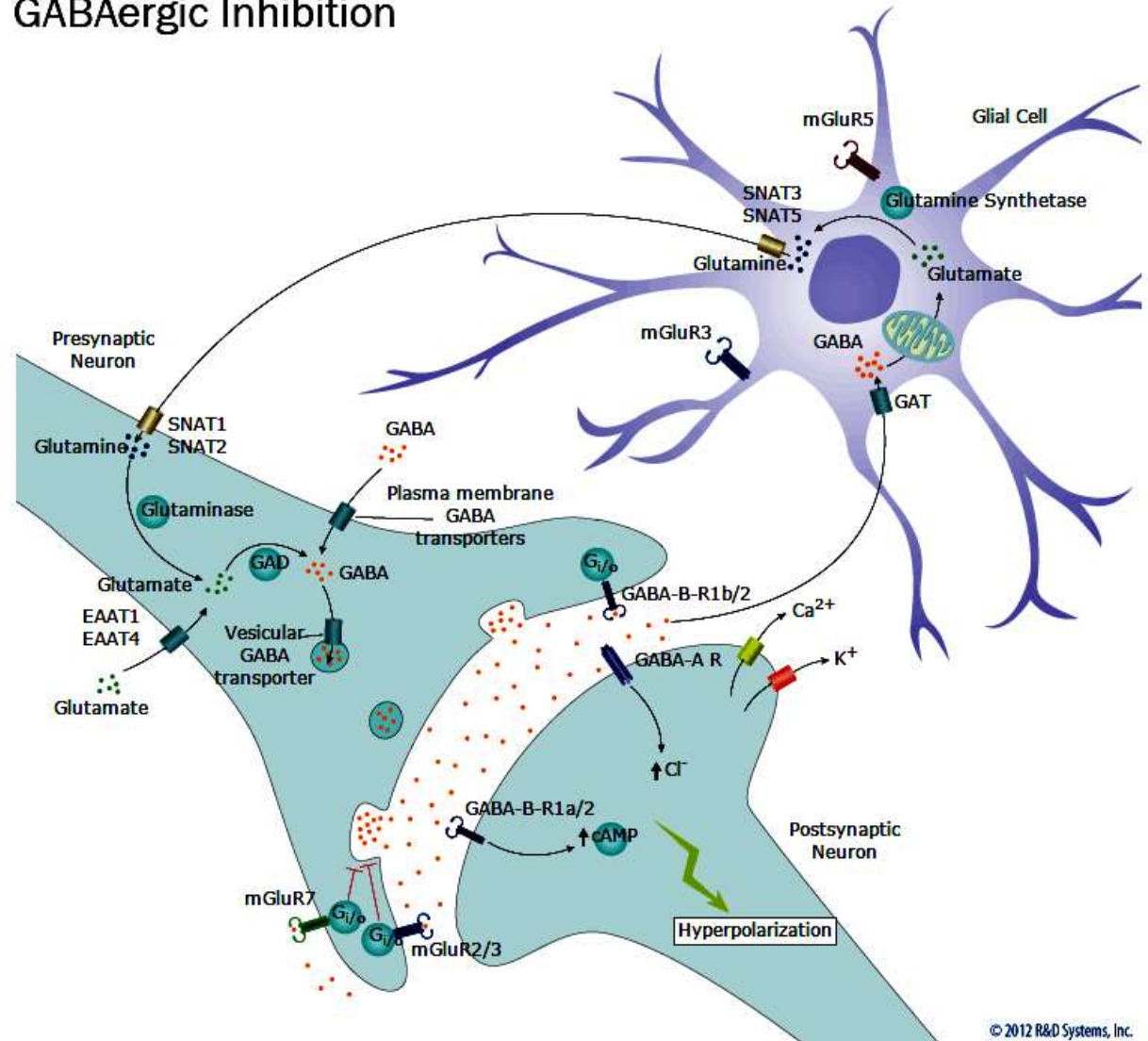
- producing drowsiness, promoting the onset and maintenance of a state of sleep that as far as possible resembles the natural sleep state.



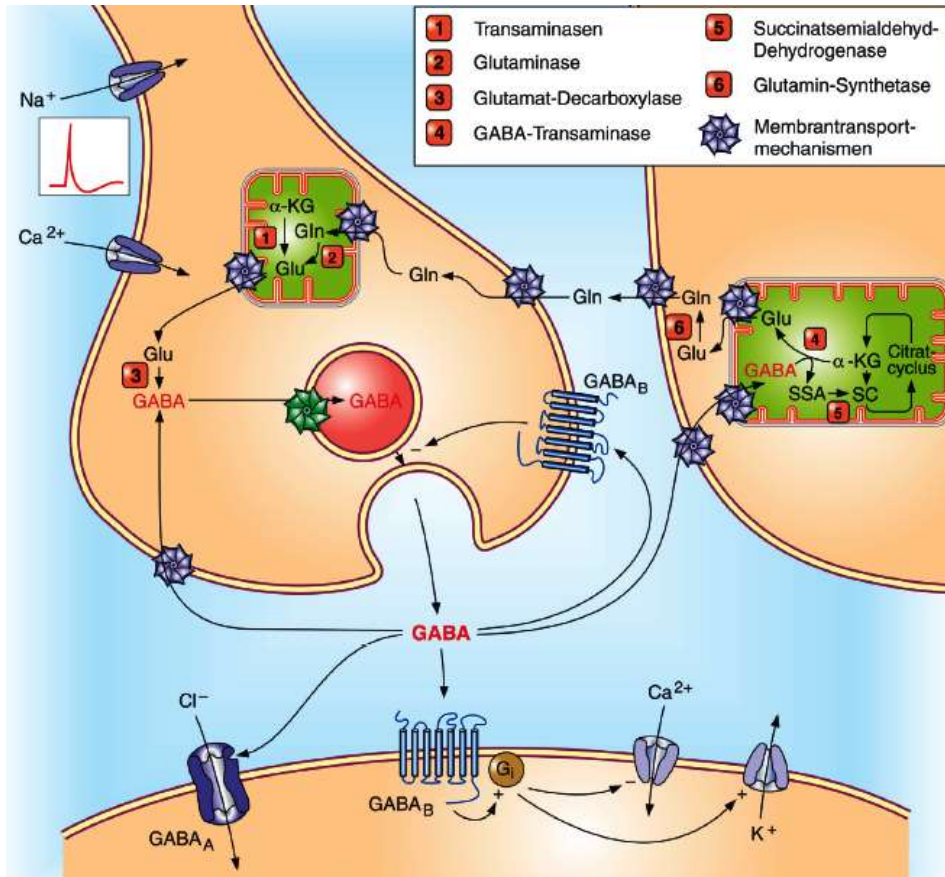
GABAergic neurotransmission

GABAergic Inhibition

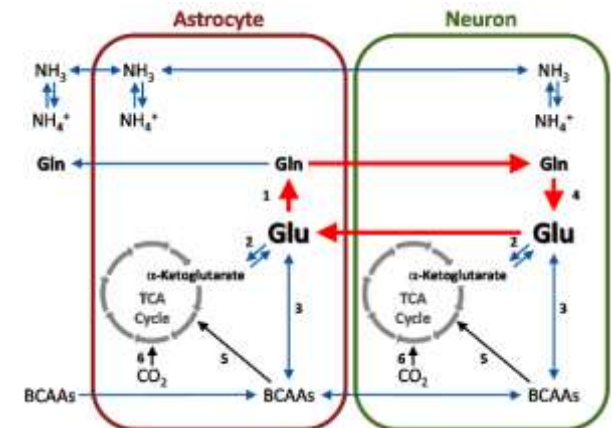
- **GABA** – most important inhibitory transmitter in the brain



GABAergic neurotransmission



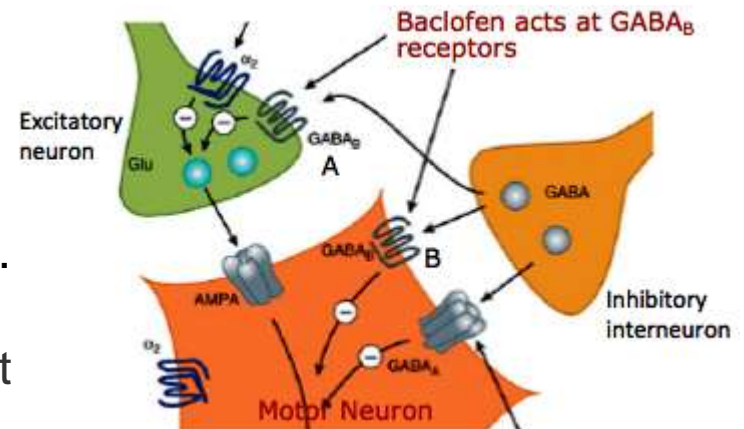
- Synthesis: from glutamate by the enzyme Glutamic Acid Decarboxylase
- Termination of action: uptake (re-uptake or glia).
- Breakdown: GABA-transaminase.
- glutamine-glutamate/GABA cycle: transfer of glutamine from astrocytes to neurons and neurotransmitter glutamate or GABA from neurons to astrocytes



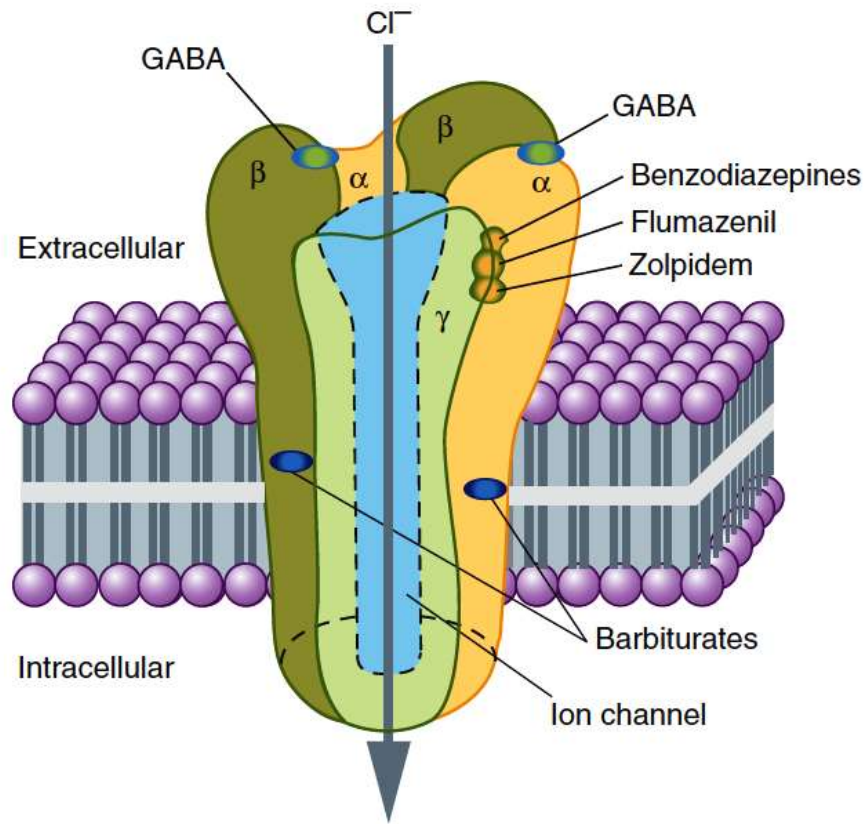
- some antiepileptics enhance the GABAergic transmission at the presynaptic site: **vigabatrin, valproate** – GABA-transaminase inhibition; **tiagabin** – GABA-uptake inhibition

GABA receptors

- **GABA_A (ionotropic)**
- **GABA_B (G-protein-coupled)**
 - **GABA_A receptors** are heteropentameric ligand-gated ion channels that permit the influx of Cl⁻ ions to decrease membrane excitability. GABA_A receptors mediate the majority of fast synaptic inhibition. GABA_A receptors are extremely important pharmacological targets. The most sedative-hypnotics act at this receptor complex.
 - Metabotropic **GABA_B receptors** are expressed on both the presynaptic and postsynaptic terminals where they inhibit neurotransmitter release and induce cell membrane hyperpolarization. GABA_B -agonist: baclofen (centrally acting skeletal muscle relaxant used in skeletal muscle spasticity).



GABA_A receptors



- Muscimol is an agonist, bicuculline is an antagonist at the GABA binding site.
- Picrotoxin is a channel-blocker (or a non-competitive antagonist).
- **Benzodiazepines** and **barbiturates** are positive allosteric modulators.

Theoretically all drugs modulating positively the GABAergic neurotransmission can cause the following actions in increasing doses:

- **anxiolytic action** (unfortunately not fully distinguishable from **sedation** – lowest dose)
- **hypnotic action** (moderate dose)
- **general anesthesia** (still higher dose)
- **coma and death** (toxic dose)

There is an additive synergism among the GABAergic or other sedatives and ethanol.

Possible additional actions of GABAergic sedative-hypnotics (not obligatory):

- **antiepileptic action**
- **skeletal muscle relaxant action**
- **amnesia**

GABA_A receptors

Subunit-composition and functional properties

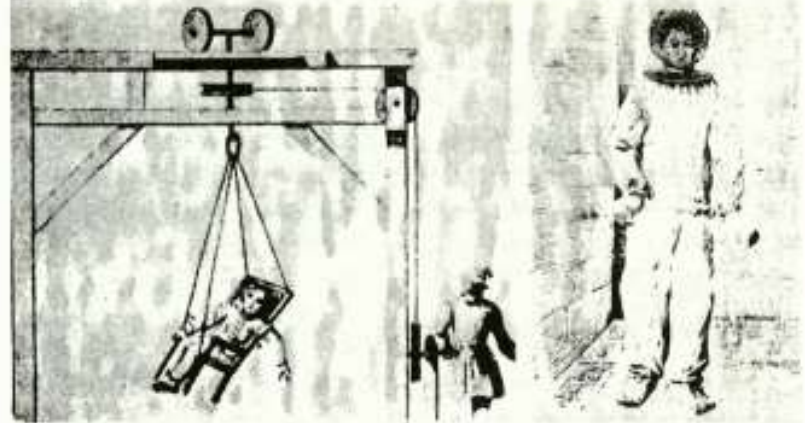
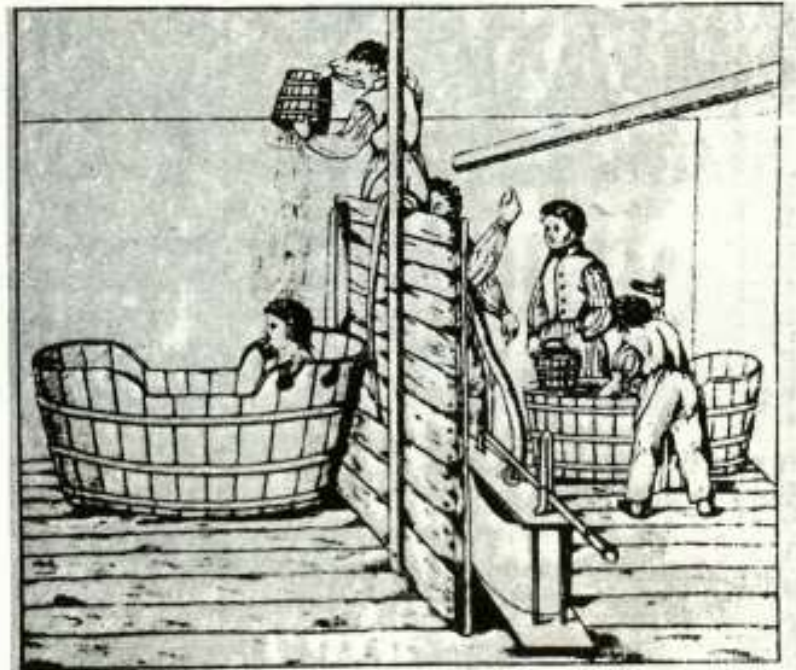
- α -subunit – importance in pharmacological effects of the positive allosteric modulators
 - GABA_A-receptors with α_1 -subunit – sedation, hypnotic effect
 - Z-hypnotics (zopiclone, zolpidem, zaleplon) - preferential affinity to binding sites at this receptor subtype.
 - GABA_A-receptors with α_2 -subunit – anxiolytic effect
 - Anxiolytic effects without sedation.
 - GABA_A-receptors with α_5 -subunit (in Hippocampus) - partial inverse agonists at the BDZ binding site: treatment of cognitive deficit ?

The past

History of the „tranquillizers”







Drastic therapy around 1800. Fifty to a hundred pails of ice-cold water are poured on the patient. Below, left: Whirling chair capable of a hundred turns a minute. Below right: Patient wearing wire mask.

Noah became a man of the ground.
He planted a vineyard, drank wine and got drunk.
(Genesis 9.20-21)



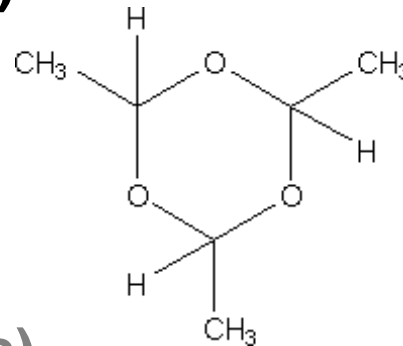
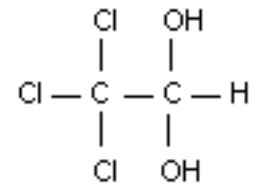


Valeriana (from the XVIth century)

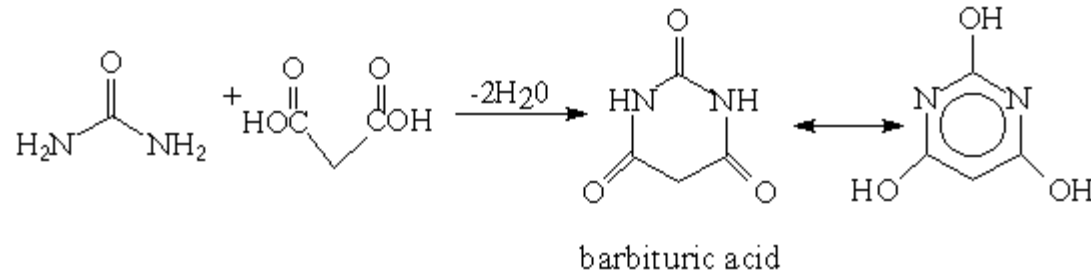


Tranquillizers in the XIXth century

- bromide
- chloral hydrate (synthesis 1832, used since 1869, the first synthetic hypnotic)
- paraldehyde (1882 – hypnotic)
- sulfonmethan (1888 – hypnotic)
- urethan (late 1800s – hypnotic)



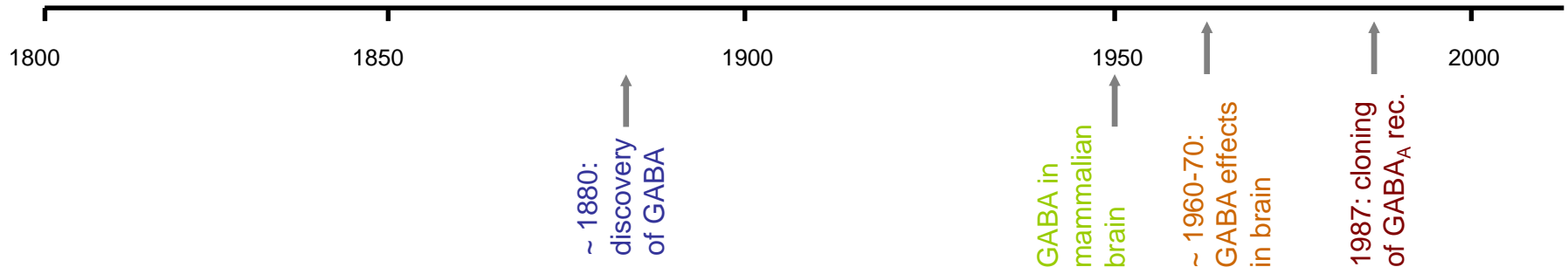
The beginning of the age of GABA: The barbiturates



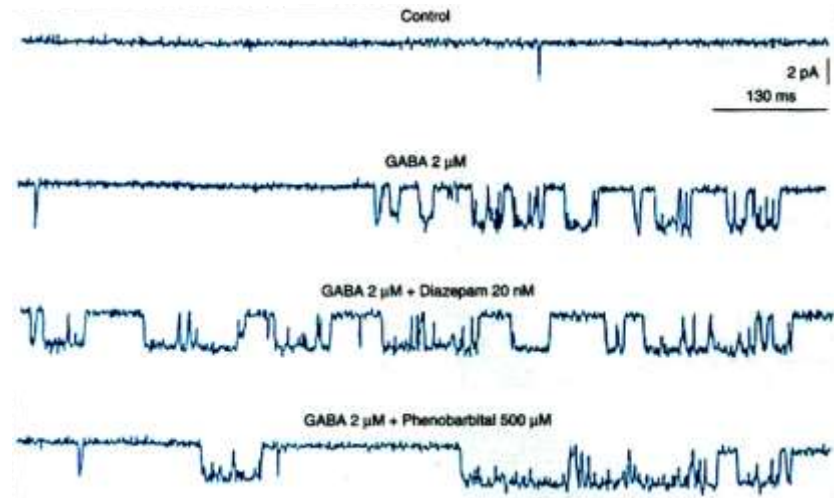
- barbituric acid – synthesized by Adolph von Baeyer 1864

- 1903 – Emil Fischer, Joseph von Mering – the first barbiturates in therapy: diethylbarbituric acid (Veronal)

1912 – Phenobarbital



Mechanism of action of barbiturates

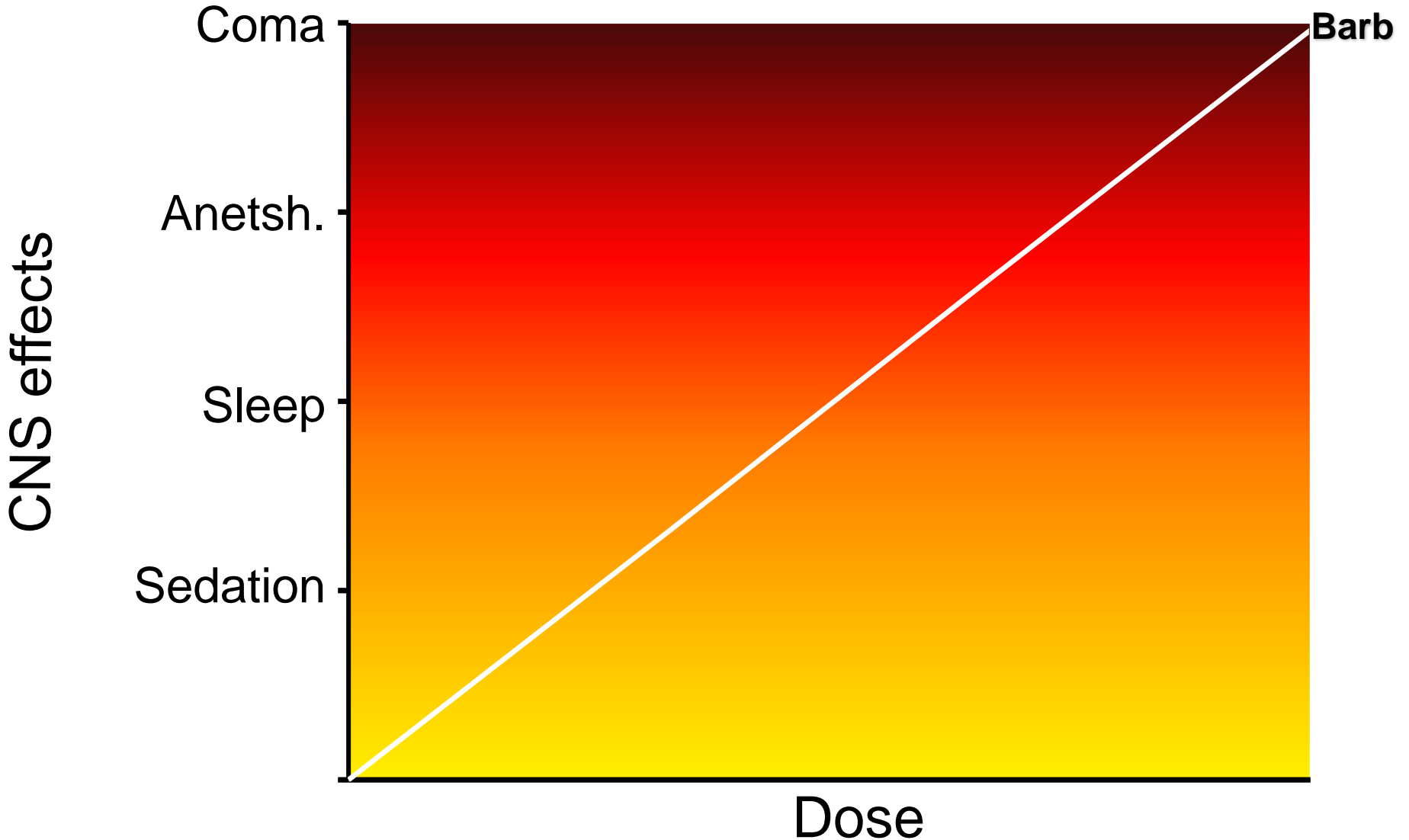


- They facilitate the actions of GABA by increasing the duration of the GABA-gated channel openings.

- At high concentrations they may activate directly the chloride channels.
- They might have further non-selective actions (depression of excitatory neurotransmission, nonsynaptic membrane effects).

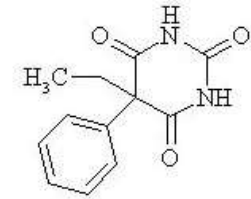
This mechanism of action explains their ability to induce full surgical anesthesia and their more pronounced central depressant effects (low margin of safety).

Dose-effect curve of GABAergic sedative-hypnotics



Long-acting barbiturates:

- **phenobarbital**
- old-fashioned sedative, hypnotic (not used for these indications), still used as an antiepileptic drug



Medium and short-acting barbiturates:

- cyclobarbital, amobarbital
- old-fashioned hypnotics

Ultra-short-acting barbiturates:

- **thiopental, methohexital, hexobarbital**
- important intravenous anesthetics
- the most important reason for their ultrashort duration of action is the redistribution from the brain into other tissues

BELBARR

AN
Excellent
 SEDATIVE
 and
 HYPNOTIC



The potentiation of the central action of phenobarbital by the belladonna alkaloids (Friedberg, Arch. f. exp. P. & P. CLX, 276) renders possible attainment of desired effects with relatively small doses, thus avoiding "hang over" and other unpleasant side-actions. In contrast to galenic preparations of belladonna, such as the tincture, Belbarr *has always the same proportion of the alkaloids.*

Indications: Neuroses, migraine, functional digestive and circulatory disturbances, vomiting of pregnancy, menopausal disturbances, hypertension, etc.

Formula: Each tablet contains $\frac{3}{4}$ grain phenobarbital and the three chief alkaloids, equivalent approximately to 8 minims of tincture of belladonna.

Belbarr No. 2 has the same alkaloidal content but $\frac{1}{4}$ grain phenobarbital per tablet.

CHARLES C. HASKELL & CO., INC., RICHMOND, VIRGINIA

the
quieting
hand

- in preoperative apprehension
- postoperative restlessness
- insomnia
- epilepsy
- hyperaesthesia
- vomiting of pregnancy
- sciatica
- hypertension
- psytic spasm
- neuritis



LUMINAL® SODIUM

BRAND OF PHENOBARBITAL SODIUM

Sedative... Hypnotic... Antispasmodic

In conditions of excitement of the nervous system, as well as in certain spasmodic affections, Luminal Sodium acts as a soothing, quieting agent to tranquilize hyperexcitability or to curb convulsive paroxysms. Small doses have a pronounced sedative and antispasmodic action. Large doses are markedly hypnotic.

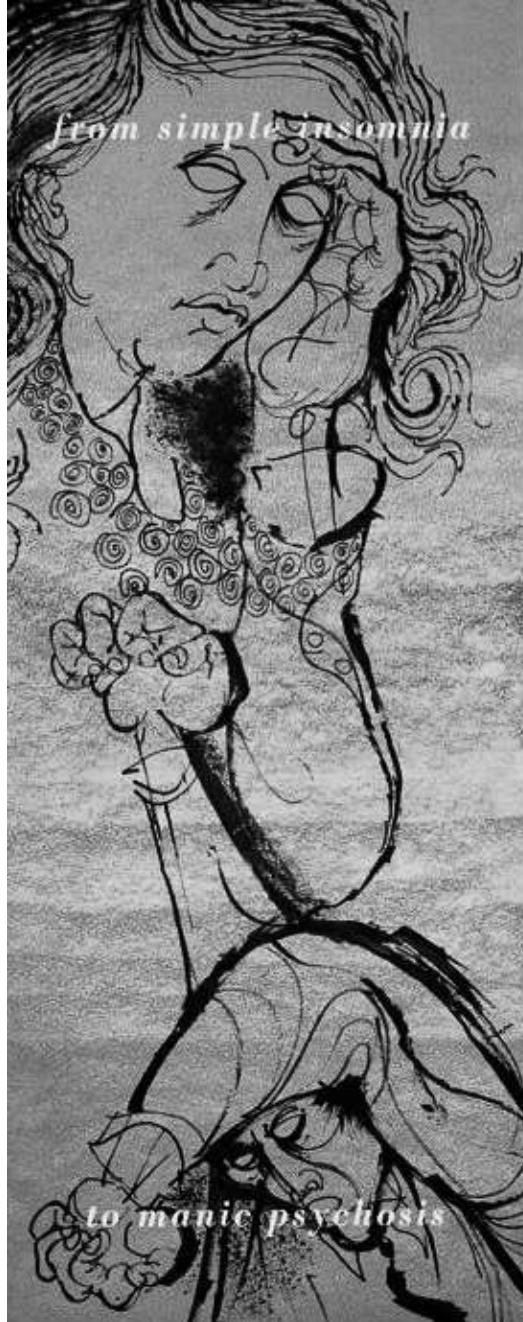
For **adult use**... solution of 16 mg. (1/4 grain), 32 mg. (1/2 grain) and 64 mg. (1 grain).

For **pediatric use**... solution in proportion of 0.32 Gm. (5 grains) to 2 cc. strength; powder 0.16 and 0.32 Gm. (2 and 5 grains) in ampuls.

Winthrop Stearns, Inc.
New York, N. Y. Wholesale Only

Luminal, trademark reg. U.S. & Canada

Phenobarbital 1954



from simple insomnia

to manic psychosis

whenever a patient needs
prompt, effective sedation...

short-acting
Nembutal®

(Pentobarbital, Abbott)

You can achieve any degree of cerebral depression using short-acting Nembutal—usually with only about one-half the dosage of many other barbiturates. This means:

- ... less drug to be inactivated,
- ... shorter duration of effect,
- ... little tendency toward hangover.

And, of course, with short-acting Nembutal you are using a thoroughly studied sedative-hypnotic with a wide margin of safety. Hundreds of clinical reports, more than 26 years of wide medical use stand behind your Nembutal prescription.

Next time—any time—a sedative or hypnotic is indicated, consider short-acting Nembutal... a standard in barbiturate therapy. **Abbott**

Pentobarbital 1956

Whatever the indication,*
whatever degree of sedation desired,
a form of Nembutal will meet the need



*OBSTETRICS—Edwards, Reeves and Whitting, America.



NEMBUTAL[®] (PENTOBARBITAL, ABBOTT)

Nothing Faster, Shorter-Acting, Safer in Oral Barbiturate Therapy!

Pentobarbital 1960

because people are different

www.aceodog.com



your obese patient needs individualized therapy

The emotional and social pressures which intensify overeating problems may vary considerably in your obese patients. Therapeutically sound individualization of antiobesity regimens is thus not only desirable, but also simply achieved with the different forms of Ambar.

Ambar
EXTENTARS® AND TABLETS
controls over-
weight & mood



Ambar + 1 Extentars provides 10-12 hours of specific suppression of food consumption, extended-action tablet: methamphetamine hydrochloride, 10.0 mg.; phenobarbital (1 gr.), 64.8 mg.
Ambar + 8 Extentars (hydrochloride) hydrochloride 10 mg., phenobarbital 1 gr. for patients who require higher maintenance strength. **Ambar Tablets** for convenient dosage of extended therapy are available in two strengths: each tablet contains methamphetamine hydrochloride, 2.82 mg.; phenobarbital 10 gr. / 23.6 mg. A. H. Robins Co., Inc., Richmond, VA, Virginia.

Metamphetamin + Phenobarbital 1959

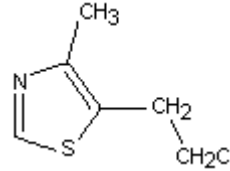
Disadvantages of barbiturates as sedative-hypnotics

- **Low safety margin (intoxication is dangerous)**
- **No antagonist**
- **Psychologic and physical dependence, tolerance**
- **Enzyme induction, drug interactions**

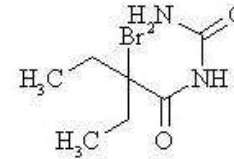


Other sedative-hypnotics in the barbiturate age

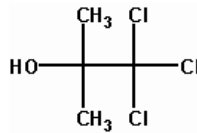
- chlomethiazole (1938)



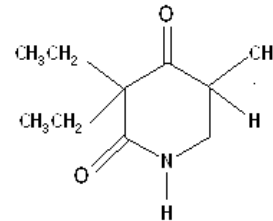
- bromisoval, carbromal (30's)



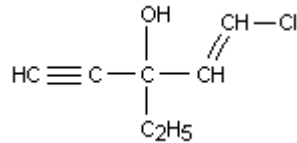
- chlorobutanol



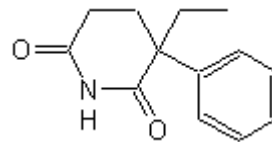
- methyprylone



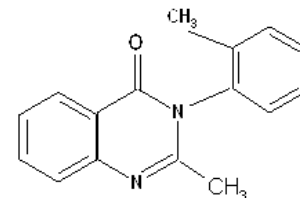
- ethchlorvynol



- glutethimide (1954)



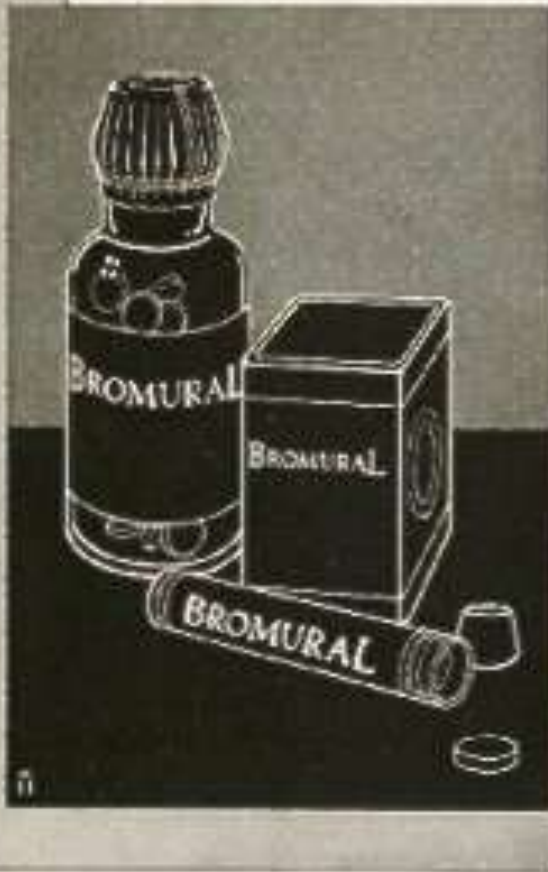
- methaqualone (1955 – by product of malaria research)



Bromural

Alphabromisovalerylcarbenide

Council Accepted



AS A ROUTINE SEDATIVE

in general nervous disturbances prescribe one tablet (5 grains) several times a day. As a mild and prompt hypnotic the dose is 2 to 3 tablets upon retiring or during the night. Bromural is not a barbiturate nor a bromide.

5 grain tablets and as a powder.

Samples and literature upon request.

Bilhuber-Knoll Corp.,

154 Ogden Avenue, JERSEY CITY, N. J.

In Answering Advertisements please mention The American Journal of Surgery

Bromisoval 1935

Sh-hh

Placidyl

(ETHCHLORVYNOL, ABBOTT)

www.docodog.com

nudges your patient to sleep

Gentle as a lullaby, this new nonbarbiturate hypnotic brings tranquil sleep, and is useful even for those patients with liver or kidney disease. 500 mg. capsules, bottles of 100.

Abbott

Ethchlorvynol 1956

why resumption of interrupted sleep is important to all your patients



12:45 a.m. Sleeping Easily



1:00 a.m. Interrupted



1:30 a.m. Rapid Resumption

Certainly Quaalude has special advantages for the patient whose sleep is interrupted. Investigators report that patients on Quaalude can be easily awakened, and that resumption of sleep is prompt and spontaneous.^{1,2,3} But what do these observations mean for your patients whose sleep is not interrupted? They mean that when you give Quaalude your patients will not be "drugged", will not have a "doped" feeling, will not suffer from morning "hangover". Rather, awakening will be easy, with a real feeling of alertness and refreshment.^{1,2}

These qualities of resumption and refreshment set Quaalude apart from the drugs you may be using now. Quaalude induces a natural, physiologic sleep of 6 to 8 hours. And isn't that what you want for *all* your patients who need your help to a good night's sleep? The secondary pharmacological actions of Quaalude—antitussive⁴ and antispasmodic⁵—suggest that it may be especially useful in insomnias complicated by cough or gastrointestinal distress. Consult product literature for complete information.

QuaaludeTM
(methaqualone)



GOOD NIGHT

PATIENTS SLEEP SOUNDLY with non-barbiturate Doriden—0.5 Gm. at bedtime. Onset of action is smooth and gradual (without preliminary excitation). Effect lasts 4 to 8 hours.



Doriden[®]

(glutethimide CIBA)

SUPPLY: Tablets, 0.125 Gm. (white), 0.25 Gm. (white, scored), and 0.5 Gm. (white, scored).

GOOD MORNING

PATIENTS AWAKE ALERT AND REFRESHED: Doriden is rapidly metabolized, allows restful natural slumber with little or no hangover.

C I B A SUMMIT, N. J. JANUARY

www.fischdog.com

Glutethimide 1957

Under the relaxing influence of nonbarbiturate Doriden, insomnia patients are usually sound asleep within 30 minutes. They awake the next morning refreshed and alert. Night-time sedation with Doriden is less restricted than barbiturates because: (1) **Doriden** is usually not contraindicated in the presence of renal and hepatic disorders; (2) Doriden rarely causes pre-excitation; (3) Doriden is metabolized quickly, thus rarely produces morning "hangover." Average dose: 0.5 Gm. at bedtime. You can also prescribe Doriden in lower dosage for daytime sedation.

DORIDEN (glutethimide, CIBA)
 SUPPLIED IN TABLETS: 0.5 Gm., 0.25 Gm., and 0.125 Gm.

C I B A
 B U M M I N G

Glutethimide 1958

Mild and persuasive as a lullaby,
nonbarbiturate Placidyl gently lulls your
patients into refreshing slumber.
Brief and effective.
Prescribe it this week and see.

Abbott

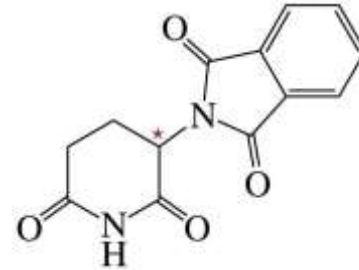


Placidyl® nudges your patient to sleep
ethchlorvynol *****

Ethchlorvynol 1959

The monster drug: thalidomid

- synthesized in 1954 in an antibiotic research program
- no antibiotic effect, but seemed to be extremely safe in animals
- searching for therapeutic effect – free samples are distributed for doctors in Germany
- patients experience sedative and hypnotic effect
- marketed in 1957 in Germany (and in 46 countries in the world) as a sedative/hypnotic as over-the-counter drug, especially advised for pregnant woman because of „unusual safety”
- the mostly used sedative-hypnotic in Germany in 1961
- withdrawn in 1961 because of teratogenic effect





»In der Schwangerschaft und Stillperiode steht der weibliche Organismus unter großer Belastung. Schlaflosigkeit, Unruhe und Spannungen sind beständige Klagen. Die Gabe eines Sedativums-Hypnotikums, das weder Mutter noch Kind schädigt, ist oft notwendig. Ein Arzt hat vielen Patientinnen in seiner gynäkologischen Abteilung und in seiner geburtshilflichen Praxis Contergan und Contergan-forte gegeben.«

1958

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales.

W. G. McBRIDE.

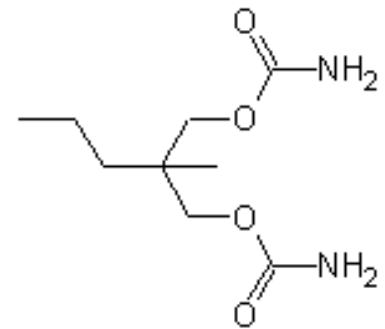
* * * In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the foetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

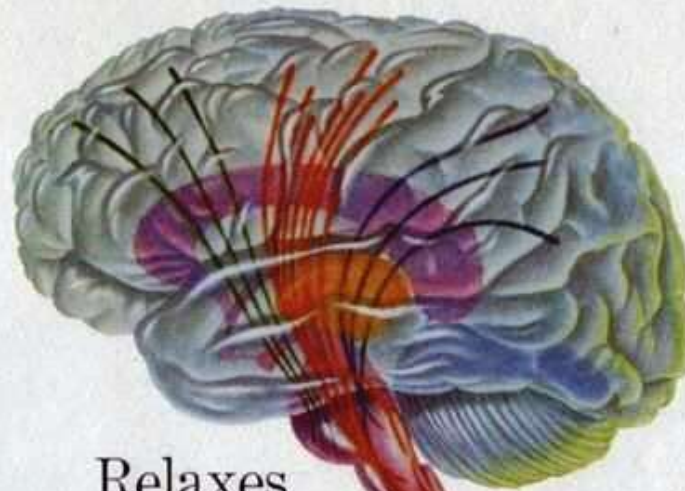
Lancet 1961

Dissociation of major and minor tranquillizers in the 50's: meprobamate and chlorpromazine

- 1952 – reserpine (used as a tranquillizer first)
- 1954 – chlorpromazine (by-product of antiallergic research program), the first antipsychotic (major tranquillizer)
- 1955 – **meprobamate** (Frank Berger) – the first minor tranquillizer

- first thought to be free from barbiturate-like adverse effects, then it became clear that it causes dependence – „dehydrated Martini”, „happy pill”, Miltown-parties – and other barbiturate-like side effects





Relaxes
both mind
and muscle

*without
impairing
mental or
physical
efficiency*

- * well suited for prolonged therapy
- * well tolerated, relatively nontoxic
- * no blood dyscrasias, liver toxicity, Parkinson-like syndrome or nasal stuffiness

*For anxiety, tension
and muscle spasm
in everyday practice.*

Supplied:
400 mg. scored tablets,
200 mg. sugar-coated tablets.
Usual dosage:
One or two
400 mg. tablets t.i.d.

Miltown

TRANQUILIZER WITH MUSCLE-RELAXANT ACTION



Meprobamate 1958

Does more than curb appetite...
also relieves the tensions of dieting



new!

Appetrol

DEXTRIO-AMPHETAMINE + MELTOWN[®]

Helps you keep your patient
on your diet

AN EXTENSIVE SURVEY shows that in 88% of overweight persons there is an emotional basis for failure to limit food intake. Appetrol has been formulated to help you overcome this problem and to keep your overweight patient on your diet.


THIS NEW ANORECTIC does more than give you dextro-amphetamine to curb your patient's appetite. It also gives you Meltown to relieve the tensions of dieting which undermine her will power.

IN PRESCRIBING APPETROL, you will find that your patient is relaxed and more easily managed so that she will stay on the diet you prescribe.

Usual Dosage: 1 or 2 tablets 3-4 times a day before meals.
Each tablet contains: 1 mg. dextro-amphetamine sulfate and 400 mg. Meltown (meprobamate, Wallace).

Available: bottles of 30 and 100 tablets.

J. Barkan, M.D. Group practitioners with the report. Paper read before The American Academy of Neurology, October, 1956.

 WALLACE LABORATORIES, New Brunswick, N. J.

Amphetamine + meprobamate

1960 – beginning of the benzodiazepine age

- Leo Sternbach (1908 – 2005)



- worked by Hoffmann-LaRoche in the USA, leader of the research program for better sedatives (1954)

- synthesized 40 compounds, all were inactive

- 1956 – his research was stopped but he synthesized the last substance: RO 5-0690, but it was not tested first

- after 18 months it was rediscovered in a shelf, tested, and was sedative, hypnotic and antiepileptic in animal studies

- it was released in 1960 as Librium, followed by Valium in 1963

